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The Hyperabduction Syndrome

With Special Reference to Its Relationship to Raynaud's Syndrome

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The hyperabduction syndrome was described in 1945. This report includes information and experience gained from the study of 52 patients suffering from its consequences and of many others in whom the diagnosis was necessarily considered. The signs and symptoms and age and sex incidence are summarized. Among the most striking findings was the fact that Raynaud's syndrome occurred in 20 of the 52 patients, an incidence far greater than anticipated in the general population. In some patients elimination of the hyperabduction position abolished Raynaud's syndrome. So far as we can determine this relationship has not been previously reported.

THE NEUROVASCULAR syndromes arising in the shoulder girdle and producing signs and symptoms in the arms and hands are frequently misdiagnosed and hence incorrectly treated. Certain well defined syndromes recognized for many years have included the cervical rib syndrome, the scalenus anticus syndrome, and inflammation of the shoulder bursa.

In 1943 Falconer and Weddell[1] described the costoclavicular syndrome, in which neurovascular complaints of the upper extremities are caused by occlusion of the subclavian artery or compression of the nerves of the brachial plexus by narrowing of the space between the clavicle and the first rib, when an individual is holding his shoulders downward and backward. This was first brought to their attention by soldiers who complained of pain, numbness and other discomfort in the arms and hands which developed during carriage of heavy packs which forced their shoulders into this position. This syndrome differs from the cervical rib and the scalenus anticus syndromes in that no abnormality of structure is involved and that the circulation in the extremity is normal when tested in a position of relaxed adduction but impaired with obliteration of the axial artery when the shoulders are forced backward and downward. This phenomenon can be temporarily reproduced in many otherwise normal persons, but is quite rare in significant degree because few people maintain the required position for long periods. Falconer and Weddell introduced a new concept, namely, that a shoulder girdle syndrome may be produced by maintenance of unusual posture without anatomic derangement.

In 1945 one of us (I.S.W.)[2] described the neurovascular syndrome produced by hyperabduction and reported 4 illustrative cases. As originally described, it was characterized by numbness and paresthesias first noticed in the finger tips and progressing centripetally to involve more of the hands and arms. Pain was curiously not a prominent feature in the original patients, even in the patient in whom gangrene developed at the tips of the fingers. Examination revealed that the pulses were ob-

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literated when the arms were hyperabducted in the supine position in which these patients usually slept. Abstinence from the position of hyperabduction produced relief from the symptoms and healing of gangrenous areas due to the impairment of circulation. Wright also demonstrated that obliteration of the pulse when the arm was elevated to a position of hyperabduction was a very common occurrence. It could be produced with varying degrees of difficulty in 83 per cent of the upper extremities of 150 normal young soldiers. In 62 per cent of right arms and 63 per cent of left arms tested, the pulses could be obliterated with relative ease. Because the first studies for normal incidence were conducted with rather husky young soldiers the question was raised as to whether heavy musculature played an important role in this phenomenon. Moses[3] later found, however, that this effect on the pulses in hyperabduction was also very common in muscularly wasted and weak patients in the older age groups and in chronically diseased patients. During the intervening years we have found this to be a very common phenomenon in patients although further attempts to obtain statistics have not been made.

In 1946 Paull[4] described another case in detail. His patient presented both the hyperabduction and the scalenus anticus syndrome. Haggart (1948)[5] described 3 cases of the hyperabduction syndrome occurring in a group of patients with various types of cervicobrachial pains. Evans (1949)[6] described a case of hyperabduction syndrome associated with the carotid sinus syndrome. This syndrome has also been included in several recent texts on peripheral vascular disease.[7–9]

The term *hyperabduction* as originally used by Wright is that phase of circumduction which brings the arms together above the head with the elbows flexed or with their long axis corresponding in plane to that of the body. Some degree of external rotation is necessary to achieve this position. While hyperabduction is accepted in anatomic terminology, it is neither ideal nor entirely logical, but is still considered to be better than any other available term. This position of hyperabduction, in contradistinction to the costoclavicular position of Falconer and Weddell, is very common and is maintained for long periods of time by many people during their sleep. It is also frequently assumed in housepainting, electrical work, automobile and airplane repair and construction work, and many other occupations, and is not an uncommon cause of symptoms.

Differentiation of Neurovascular Syndromes Arising in the Shoulder

Symptoms attributable to cervical rib, scalenus anticus syndrome, Falconer and Weddell's syndrome and the hyperabduction syndrome are similar. Although each is dependent upon intermittent pressure on vessels and nerves, the mechanism of production differs and must be clearly understood if treatment is to be effective. Frequently one individual may have symptoms attributable to more than one mechanism.

Methods of Testing for the Hyperabduction Syndrome

While the evidence seems convincing that this syndrome is due to pressure on both the nervous and vascular supplies to the upper extremities, it is difficult to do satisfactory quantitative tests for intermittent pressure on the nerves to the upper extremity. Reflex and sensory studies with the arms in various positions have thus far not been very revealing but more detailed studies might well be profitable. It is, however, simple to test for the occlusion of the major arteries to the upper extremity by two methods. First the patency of both the radial and ulnar arteries should be tested by means of the Allen test in which the patient elevates his hands, makes a tight fist and the observer occludes both the radial and ulnar arteries by pressure with his thumbs over these vessels at the wrist. The hand is then lowered to a dependent position and the patient is asked to open his fist. The arteries are released one at a time. Patency of each artery is separately demonstrated by a flush of blood into the pale skin of the hand.

The first method of testing for the hyperabduction syndrome used by Wright consists of having the examiner place his fingers on the radial pulse of the patient with his arm at his side at ease (adduction). The patient should sit in a straight-backed chair with the observer standing behind the patient. The observer then passively moves the patient's arm through a 180 degree semicircle keeping his fingers on the pulse all the time and noting where this diminishes and where it can no longer be felt. This should then be checked with the patient in the supine posi-

tion. This has advantages in that it requires no special equipment, and is therefore readily available to all physicians. It has some limitations in that it is frequently difficult to determine whether there is a substantial diminution of a pulse that is not completely obliterated. We have noted in experimental observations that frequently there is a reduction to approximately one-tenth of the usual arterial oscillometric readings at the wrist before an observer can denote an appreciable difference in the strength of the radial pulse. With the movement involved in this test the observer will often lose the pulse by the movement of his fingers and he must be certain by rechecking several times that there actually is an interruption of the pulse in a specific position.

The second and more objective method of determining the occlusion of the pulse by this maneuver is to place an oscillometer on the wrist and adjust the pressure to the point of maximum oscillation. The arm should then be moved passively through a 180 degree semicircle noting the oscillometric readings at the 0, 45, 90, 135 and 180 degree marks. It is necessary to move the oscillometer with the arm in order to avoid stress or torsion of the tubing.

It is advisable from the standpoint of complete diagnosis to test for all associated conditions at the same time. This can be done by (1) pulling down on the arm in the position of adduction while the patient at the same time forces his shoulder back to test for the costoclavicular syndrome; (2) by having the patient turn his neck sharply to the right and to the left and then breath deeply, with the arm at 45 degree abduction, the observer meanwhile noting the readings in order to test for scalenus anticus and cervical rib syndromes.

With this technic, in a typical case of the hyperabduction syndrome the readings in table 1 were obtained. On the left side, the oscillations dropped to zero at 100 degrees of abduction. The right arm had to be placed in full hyperabduction before the oscillometric readings became markedly diminished, but once reduced they did not return to normal for several minutes after the arm resumed the position of relaxed adduction. This is a rather important observation. It represents a significant abnormality due to continuing spasm of the arteries after the irritating stimulus has been removed. This has been observed clinically as the phenomenon of persistant symptoms. Such observations must be carefully rechecked to be certain that they are not due to artefacts associated with the use of the oscillometer and its rubber tubing. This method of testing for the pulsations at the wrist has the advantage that it is objective, that gradual or abrupt blockage can be differentiated, and that the postcompression spasm of the arteries can be better evaluated. The release of this postcompression spasm is striking when one observes an immobile oscillometer needle gradually start to oscillate without a change in the patient's position.

Criteria for Diagnosis of the Hyperabduction Syndrome

Since, as Wright originally pointed out, the majority of all adults have an anatomic construction which can produce obliteration of the pulses of the arm in the position of hyperabduction, some criteria must be adopted whereby this condition is considered pathologic in a given patient. The following criteria for the diagnosis of the *hyperabduction syndrome* are therefore suggested:

1. The presence of symptoms or signs suggesting some neurovascular disturbance of the upper extemity (symptoms and signs are discussed in detail later in this paper).

2. The demonstration that the pulse is obliterated in the position of hyperabduction or that the symptoms of a neurologic disturbance become aggravated in the hyperabduction position.

TABLE 1.—*Oscillometric Readings at Wrist*

Degrees from Adduction; Other Maneuvers	Right	Left
0	4.0	2.5
45	4.0	2.5
90	4.0	2.5
135	4.0	0*
180	0.2	0*
Costoclavicular maneuver	4.0	2.5
Head turned to opposite side	1.0	0.2
Deep inspiration	4.0	2.5

* Complete obliteration of pulse.

3. Evidence that the patient assumes the position of hyperabduction for considerable periods of time either at work or in sleep.

4. Cessation or marked diminution of symptomatology following the abandoning of the position of hyperabduction. This is frequently dramatic especially if the major symptoms and signs have arisen from intermittent arterial embarrassment. It may take much longer if the nerves have been seriously damaged.

If venous thrombosis has occurred as a result of hyperabduction edema may be persistent.

Criteria for the Diagnosis of the Costoclavicular Syndrome

1. Symptomatology of a neurovascular syndrome of the upper extremity.

2. The demonstration of obliteration of the pulse or aggravation of the neurologic symptoms when the shoulders are forced backward and downward.

3. Evidence that the patient maintains this position for considerable periods of time.

4. Evidence that when corrective postural methods have been instituted relief of symptoms occurred. This is not always easily obtainable.

Criteria for the Diagnosis of Cervical Rib Syndrome

1. Demonstration of cervical rib by x-ray. The diagnosis of the presence of a cervical rib is only in part an x-ray diagnosis. The fact that a cervical rib is definitely present on x-ray does not confirm or disprove the presence of the syndrome because the majority of cervical ribs produce no symptoms. Contrariwise, the absence of a visible cervical rib on x-ray does not exclude the diagnosis, since a residual fibrous band which is radiolucent can cause the characteristic symptoms.

2. Neurologic findings such as changes of the reflexes and sensory disturbances are frequently found associated with cervical ribs, but to justify this diagnosis and before embarking on a surgical procedure the patient should present symptoms which logically could be caused by this abnormality. The maneuvers to determine the likelihood of a cervical rib syndrome are similar to those used for the scalenus anticus syndrome and are discussed under that section. A serious effort should also be made to determine the possibility of the symptoms being due to the other syndromes under discussion.

3. Relief following surgical removal of the rib constitutes conclusive evidence of the relationship of symptoms to the cervical rib or band.

Criteria for the Diagnosis of the Scalenus Anticus Syndrome

The scalenus anticus is the most difficult of all of these syndromes to diagnose with certainty before operation. It is wiser therefore to study the patient first for the other three syndromes and then to attempt to analyze the problem from the viewpoint of the scalenus anticus syndrome. The criteria for this syndrome are the following:

1. The presence of symptomatology of a neurovascular disturbance of the upper extremity.

2. Obliteration of the pulses or aggravation of the neurologic symptoms by turning the head forcibly to the side away from that being tested (occasionally on turning toward the side being tested). This may also be aggravated by deep inspiration.

3. Evidence of hypertrophy or tenderness of the scalenus anticus muscle.

4. Relief following section of the scalenus anticus muscle (sometimes by the injection of Novacaine into the belly of the muscle).

Differential Diagnosis of Shoulder Girdle Syndromes from Other Conditions

It should be borne in mind that the hyperabduction and other shoulder girdle syndromes may play a part in the production of pains in the shoulders and arms of patients with coronary insufficiency and myocardial infarction.

Pain in the left arm is regarded as a common symptom of myocardial disease. Edeiken and Wolferth,[10] Shapiro, Lipkis and Kahn,[11] Johnson[12] and others have stressed this relationship. Prolonged hyperabduction of the arm during a profound illness with heavy sedation may, however, produce a shoulder-arm syndrome.

Many other conditions may produce shoulder-arm-hand syndromes. Excellent reviews of this subject have been published by Haggart,[5] and Steinbrocker, Spitzer and Friedman.[13]

A partial list of these conditions is seen in table 2. They must be borne in mind in establishing the diagnosis of the hyperabduction syndrome. The differential diagnosis is not usually difficult if the findings are carefully analyzed.

Present Study and Findings

This presentation includes data gathered from patients suffering from symptoms in the upper extremity as a result of or aggravated by prolonged hyperabduction of the arms. Until recently the attention of physicians had not been focused on the need for a careful differ-

ential diagnosis of shoulder girdle syndromes. Therefore hospital records more than three or four years old have been found to be of little value for this study.

In several of our patients, prolonged bed rest due to other diseases resulted in the arms being in a position of hyperabduction for prolonged periods of time with development of the typical symptoms. One patient has never had symptoms except following surgery for an unrelated condition. During the operation his arms were in a position of hyperabduction.

In this series, sex and age in adulthood have had no ascertainable effect on the incidence of the condition. We have encountered no cases in young children thus far. In this connection it will be recalled that the incidence of cervical rib and scalenus anticus syndromes increases in the 30 to 50 year age group. Even though a congenital anomaly is present in these syndromes, the symptoms usually do not occur until middle life when muscles begin to relax and structures sag.

In the present series the age of onset is shown in table 3. The youngest case was 16 and oldest was 69. The onset appeared to be more closely related to the habitual assumption of the position of hyperabduction at work or sleep than to other factors which are coincidental with aging. All patients except 4 had definite evidence of occlusion of the major arteries to the upper extremity in positions of hyperabduction. These 4 patients developed aggravated symptomatology in the position of hyperabduction probably on the basis of compression of the brachial plexus.

The great majority (34) of our patients habitually slept in the position of hyperabduction. Some stated that it was difficult to be certain how much of the time was spent in that position but they were certain that they were in it at times. A smaller number were not aware of sleeping in this position but their husbands or wives observed that they did. Seven worked with their arms in abduction or hyperabduction. One of these taught ballet dancing. The second had been a stock clerk constantly reaching for materials on high shelves. The third was a drill press operator and the fourth a machinist. The fifth was a

TABLE 2.—*Classification of Disorders of the Shoulder Girdle and Upper Extremity for Use in Differential Diagnosis*

Neurovascular
- Hyperabduction syndrome
- Cervical rib syndrome
- Scalenus anticus syndrome
- Costoclavicular syndrome
- Sclerodactylia associated with myocardial ischemia
- Raynaud's phenomena
- Scleroderma
- Neurovascular syndromes due to abnormal first rib, cervicodorsal scoliosis or arthritis, post-traumatic or postpolio defects and poor posture

Predominantly Vascular
- Raynaud's phenomena
- Thromboangiitis obliterans
- Pernio
- Migratory thrombophlebitis
- Primary axillary venous thrombosis
- Diffuse vasculitis

Predominantly Neurologic
- Sympathetic dystrophy
- Post-traumatic osteoporosis (loosely classified as Sudeck's atrophy)
- Herpes zoster (postherpetic)
- Posthemiplegia dystrophies
- Dupuytren's contracture
- Causalgia
- Herniated nucleus palposus (cervical)
- Peripheral neuritis
- Syringomyelia
- Cord tumors
- Crutch palsy
- Saturday night palsy

Miscellaneous
- Osteoarthritis, especially cervical
- Myofascitis, primary
- Myofascitis, secondary to osteoarthritis
- Dermatomyositis
- Nodular panniculitis
- Subdeltoid bursitis
- Calcium deposits in tendons or other soft tissues

TABLE 3.—*Sex and Age Incidence of Hyperabduction Syndrome*

Sex

Female	28
Male	24
Age	*No. of Cases*
16–20 yrs.	5
20–30	6
30–40	14
40–50	13
50–60	11
60–69	3

nurse holding retractors, the sixth a short surgeon, and the seventh a metal polisher who leaned with his arms at 135 degree angles to add body weight to his electric buffer.

Signs and Symptoms

The patients in this series included only those whose primary symptoms were caused or aggravated by the position of hyperabduction. We have not included a much larger group of patients in whom obliteration of the pulse in hyperabduction was an incidental finding, and who had no real symptoms related to it.

The symptoms differed somewhat from those usually found in connection with occlusive arterial diseases due to the facts that (a) the occlusion was intermittent, and (b) no inflammatory or arteriosclerotic changes were present in the vessel walls early in the development of the syndrome.

TABLE 4.—*Signs and Symptoms of the Hyperabduction Syndrome (52 Patients)*

1. Pain or aching (total patients 30)	
Hand	27
Arm	7
Shoulder	11
Shoulder-hand	9
2. Numbness	26
3. Raynaud's phenomenon (total patients 20)	
female	14
male	6
4. Paresthesias	18
5. Rubor and/or swelling of hands	12
6. Weakness	8
7. Ulceration of finger tips	2

Many patients had two or more of these signs or symptoms.

Pain which occurred in 30 of the 52 patients was the most common but a variable symptom. It was described as aching in character, extreme discomfort, or an inability to find a comfortable position. It was very prominent in the hand in 27 cases, in the shoulder in 11, both shoulder and hand in 9 and in the arm in 7. Some patients had pain in more than one area.

Numbness. Numbness involving the fingers or hand was noted in 26 patients. In the more severe cases it involved the forearm and occasionally part of the arm but rarely extending as high as the deltoid muscle.

Raynaud's Syndrome. This study demonstrated for the first time that Raynaud's syndrome is frequently associated with and may be produced by the hyperabduction syndrome. This relationship occurred in 20 of 52 patients. The attacks were frequently mild in nature but were severe in some cases. They differed in no way from classic descriptions of Raynaud's syndrome. They were precipitated by cold and by emotional imbalance, but occurred much more frequently in the morning and in some cases only in the morning shortly after awakening from sleeping with the arms in hyperabduction.

Several patients have ceased having attacks of the Raynaud's syndrome when they stopped sleeping with their arms in hyperabduction. For example, J. O'T., a 16 year old seminary student, noted blanching of the left second, third and fourth fingers, brought on by exposure to cold. This was followed by hyperemia in a warm environment. Oscillometric readings taken at the wrist were zero when his arms were hyperabducted above 100 degrees. A typical Raynaud's phenomenon was readily produced by placing his hands in water at 4 C. Questioning revealed that he had developed the habit of sleeping on his back with his hands behind his head. In this position his arterial pulsations were obliterated. After he was instructed to cease sleeping with his arms in hyperabduction he went through the entire winter without an attack of Raynaud's syndrome in contrast with the occurrence of countless attacks the previous winter and the occurence of attacks during the summer while swimming.

Since we have become aware of this hitherto unrecognized relationship we have found many patients with Raynaud's syndrome who have had the physical findings of the hyperabduction phenomenon. It appears that in certain vasolabile individuals the hyperabduction syndrome is a major precipitating or aggravating factor toward the development of the Raynaud's syndrome.

Paresthesias. Paresthesias, usually consisting of the sensation of pins and needles, but occasionally as formication, were grouped together as a common complaint. They were

present in 18 patients. They are probably frequently confused with numbness by the patients. Eleven of these 18 are also included above in the category of numbness.

Discoloration and Swelling of Hands. Twelve patients complained of the appearance of their hands. The hands were red in all of these and swollen in most. The rubor on dependency appears like that commonly seen in obliterative arterial disease and may be quite intense. Pallor on elevation of the hands occurred rarely.

Weakness. Weakness was mentioned not infrequently. It was so serious that 8 patients were unable to grasp articles. Often prominent upon arising in the early morning, it tended to disappear promptly. It also occurred when the hands were held in the hyperabducted position. For example, 3 women complained that they could not set their hair properly because of the weakness and discomfort which developed when their arms were hyperabducted. This resembled the complaints of others who worked with their arms in hyperabduction.

Ulceration. Two patients developed ulcerations at the tips of their fingers. These promptly healed when hyperabduction of the arms was avoided.

Illustrative Case Reports

Very Mild

This group was not included in this series but should be briefly mentioned. It consists of a very large group of normal people who sleep with their arms in the position of hyperabduction for short periods of time and are then semiaroused by numbness or pain in the arms. They change to a more comfortable position and the incident is often forgotten. Such individuals develop more marked symptoms if they remain in a position producing arterial occlusion or pinching of the nerves over a long period of time such as in an alcoholic or anesthetic state.

Mild Symptoms

Mrs. L. D., case 6, was a 40 year old housewife who complained of numbness, a sensation of pins and needles, and pains in both hands and wrists. The pain was often very severe. It occurred almost exclusively at night and she noticed that it would disappear if she got up and walked about. She frequently developed Raynaud's syndrome. Her general physical examination, including a detailed vascular examination, was unremarkable except for the signs mentioned below.

Oscillometric readings taken at the wrist are recorded in table 5.

Table 5.—*Oscillometric Readings at Wrist*

Patient	Degrees from Adduction; Other Maneuvers	Right Wrist	Left Wrist
L. D.	0	2.2	2.5
	45	2.2	2.5
	90	2.2	2.5
	135	1.0	1.2*
	180	0.3	0.4†
	Costoclavicular maneuver	2.2	0.8
	Head turned to opposite side	1.2	2.0
	Deep inspiration	0.5	2.0
B. K.	0	1.2	1.5
	45	0.9	0.5
	90	0.2	0.1
	135	0.1	0
	180	0‡	0
R. B.	0	1.1	1.0
	180	0	0
R. L.	0	1.8	1.2
	180	0.1	0.3
A. W.	0	1.5	1.5
	45	1.2	1.2
	90	1.0	0.8
	135	0.8	0.4
	180	0.3	0.1
	Costoclavicular maneuver	0.3	0.2
	Head turned to opposite side	0.3	0.1
	Deep inspiration	0.3	0.1

* Graded decrease.
† Marked diminution.
‡ Complete obliteration of pulse.

When her hands were placed in ice water her fingers turned cyanotic and then pale. After removal from the water they developed the typical erythema, thus completing Raynaud's syndrome. The syndrome was of mild degree. X-ray examination showed that no cervical rib was present. On further questioning, it was revealed that she always slept on her back with both hands in hyperabduction. She had little trouble changing this habit, and since sleeping with her hands at her sides she has had no

symptoms and no recurrence of the Raynaud's syndrome for over two years.

This case illustrates the type of results usually obtained in uncomplicated cases.

Moderately Severe

Mrs. B. K., case 4, was a 32 year old teacher of ballet dancing who complained of pain in her right shoulder and arm and to a lesser degree in the left. Two years before she came under our care she was treated for a "thrombosis of her right axillary vein." Even before then she had noticed that her arms would tingle when she kept them above her head for long periods for teaching purposes. She has had Raynaud's phenomena for some years, precipitated by cold. Trophic changes developed at the tips of her fingers. She stated that she could not go to sleep with her arms in a position of hyperabduction but that she might unconsciously assume that position. She has never been awakened by symptoms in her arms. For two years she noticed that her hands and fingers were puffy, and that they are almost constantly red and slightly tender. She described them as "dishpan hands" although that etiology was ruled out in her case. X-ray studies were negative for cervical rib. Oscillometric readings at her wrist are recorded in table 5.

The significance of these findings was explained to this young woman, but in spite of the severe symptoms, and obvious trophic changes, she felt that her career was more important at the present and she would not abandon it. It was estimated that she spent at least four hours each day in positions in which she had no measurable pulsations in her arms. As was anticipated, various types of physiotherapy were of no avail. Procaine injections in what appeared to be trigger areas were tried without success. Unless this patient changes her occupational habits it is expected that her condition will remain the same or become progressively worse.

Severe Symptoms

Mrs. R. B., case 1, is a 22 year old housewife with very labile emotions. She had noted for some time that her hands were white and cold when she awakened in the morning. She always slept with her arms in a position of hyperabduction. Two years ago, coinciding with a marital crisis, she developed a typical Raynaud's syndrome after which both hands were noted to be swollen. The tips of the fingers became very tender and painful. Within a few weeks her left second finger became blue and a deep, very painful ulcer developed at the tip. One month later her right hand became involved and within several months an ulcer appeared at the tip of her right third finger. Her left second finger nearly healed in the meanwhile but was still very tender. Attacks of Raynaud's syndrome continued to occur, aggravating the condition of her fingers.

On examination there was an area of necrosis at the tip of the left second finger and a small shallow very indolent looking ulcer on the tip of the right third finger. There was no appreciable evidence of inflammation about this ulcer. Oscillometric readings are in table 5. Raynaud's phenomenon was produced by placing her hands in water at 4 C. Thirty days after being advised to sleep with her hands at her sides she returned saying that she had experienced *no* new attacks of Raynaud's syndrome. When she awoke in the morning her hands were now pink and warm in contrast to their previous cold and white appearance. The ulcers were completely healed and she had no more pain. Now, two years later she remains symptom free. She has almost completely broken the habit of sleeping in hyperabduction although she does awaken in this position about once a month. Occasionally her hands become somewhat cyanotic if they are cold and she believes that they become cold more easily than normal. She has however had no further attacks typical of Raynaud's syndrome.

The Hyperabduction Syndrome as a Complication of Other Disease

In addition to these relatively pure examples of the hyperabduction syndrome with and without the Raynaud's syndrome, there are many individuals who have a disability of some other type involving their upper extremity, which is complicated by hyperabduction. These disabilities may be of many different etiologies, vascular and otherwise.

Occlusive Vascular Disease

In the presence of an occlusive vascular disease, as in thromboangiitis obliterans, additional impairment by hyperabduction can produce marked aggravation of the ischemia.

Case 36, R. L., a 28 year old man, developed a painful callus at the tip of his right second finger. This was excised but the callus reformed and finally ulcerated. He then noticed that both index fingers began to blanch in cold weather or under emotional stress. The pain in the second right finger became increasingly severe and he went to many physicians without obtaining relief. The diagnosis of thromboangiitis obliterans was established. One dorsalis pedis pulse was found to be absent. His feet developed marked rubor on dependency and pallor on elevation. When first seen by us he had a normal Allen test indicating that in adduction both the radial and ulnar arteries were functioning down into the hand.

Oscillometric readings at the wrists are shown in table 5. He was a heavy smoker and in spite of advice to the contrary he continued to smoke. Later his right ulnar artery became occluded and the oscillometric readings of his feet became progressively less.

This man had been in the habit of sleeping on his right side with his right arm hyperabducted under his pillow. The aggravation of his circulatory deficiency probably precipitated the ulceration at an earlier date than it would have occurred on the basis of the thromboangiitis obliterans alone, thus calling attention to the underlying but previously unrecognized disease.

When the patient learned to sleep without his hands in the position of hyperabduction his pain promptly lessened and the ulcer healed. This occurred in spite of the fact that he continued to smoke and while evidences of further advancement of the thromboangiitis obliterans were occurring elsewhere in his vascular system.

Axillary Venous Thrombosis

During the past year we have encountered 4 cases of axillary venous thrombosis associated with the hyperabduction syndrome. The etiology and mechanism responsible for axillary venous thrombosis has frequently been difficult to determine. Our observations lead us to believe that at least in some cases it is related to an arrangement in the structure of the shoulder girdle which produces unusual pinching and torsion of the subclavian or axillary vein with relatively minor strains.

As an example, A. W., a 49 year old prison guard, suddenly developed pain and swelling of his right arm after pulling on a heavy prison door which had become stuck. He had developed a very definite thrombosis of the axillary vein. Months later the residual swelling was present. The oscillometric readings obtained are shown in table 5.

It is thus clearly demonstrated that the hyperabduction, the costoclavicular and the scalenus maneuvers produce marked compression of the subclavian artery. It is likely that pinching of the adjacent vein is also easily produced by similar measures. Sudden forcible pressure apparently did produce compression of the vein with temporary blockage and later thrombosis. The endothelium may well have been traumatized at the time of the strain encouraging the production of the thrombus.

ANATOMIC CONSIDERATIONS

It was noted by Wright[2] that many individuals can obliterate their radial and ulnar pulses by muscular contraction of the shoulder and arm muscles when the arm is in a position near that at which slight additional abduction causes obliteration of the pulse. Further observations have since confirmed this fact. In addition we have encountered several patients who have been able to obliterate their pulses with their arms in almost any position by contraction of the pectoralis major and minor muscles. Others can block their pulses with the arms in a marginal position by deep respiration or by turning their heads away from the arm being examined. Of the 150 individuals above mentioned questioning revealed that 13 of them frequently slept with their arms hyperabducted. Six of these slept very comfortably in this position. In these 6 obliteration could be produced only with difficulty and not in the position in which they usually slept. Seven frequently fell asleep with their arms hyperabducted but soon developed sufficient discomfort to bring their arms down below the shoulder level. In 6 of these subjects obliteration of the pulses was easy to accomplish by hyperabduction and occurred in the sleeping position which produced the symptoms. One person developed numbness in the right hand in a position of hyperabduction without obliteration of pulse. This was considered to be on the basis of pinching of certain trunks of the brachial plexus. Since obliteration of the pulses with hyperabduction of the arms is a very common phenomenon it is not surprising that this syndrome is frequently recognized when the possibility is borne in mind. The fact that obliteration of the pulses could be produced in 83 per cent of normal subjects indicates that the mechanism is based on what must be considered as normal structural components and relationships thus differing from cervical rib or the scalenus anticus syndrome. When pathologic changes occur in the extremities they must result from prolonged occlusion of the arteries or veins and damage to the nerve trunks caused by stretching, pinching, prolonged ischemia or all three.

The dissections carried out by Moolten[2] clari-

fied the mechanism responsible for this syndrome (figs. 1 and 2). They reveal two points of torsion, stretching and pinching which either alone or jointly appear to play major roles in most cases. One is the point of transition at which the subclavian artery and vein become the axillary artery and vein and the main trunks of the brachial plexus pass posterior to the pectoralis minor just beneath the coracoid process. Here the vessels and nerves are relaxed and well protected in adduction but when the arm is hyperabducted they are stretched around and underneath the coracoid process. By the same action the pectoralis minor is drawn tight. The double action results in different degrees of stretching, torsion and pinching of the artery vein and nerves in different individuals.

The second point of pressure and torsion produced by certain positions of the arms and shoulders is where the artery, vein and plexus pass between the clavicle and the first rib. Clinical observations emphasize that the syndromes complained of by many of these patients may be due to pinching of the local arteries, veins, and nerves supplying the structures in this region. This is confirmed by the marked relief which frequently follows abandoning the position of hyperabduction. For a more complete discussion of these mechanisms the reader is referred to the original paper.[2] The hypothesis was advanced that in the absence of occlusion of the pulses in the position of hyperabduction most of the symptoms are due to the stretching and pinching of nerves and to the ischemia of nerves as a result of whole or partial occlusion of the nutrient vessels. In patients in whom the pulses are occluded by hyperabduction and in whom marked changes, including gangrene or other trophic changes, occur, the signs and symptoms are due in part to tissue ischemia. Six years of additional observations appear to confirm these conclusions.

Considerations for Prevention and Treatment

Briefly stated, preventive and therapeutic measures consist of maintaining adequate circulation and unimpeded nervous supply into the upper extremities at all times.

The pure hyperabduction syndrome can be prevented or eliminated by having the patient avoid the precipitating position during his work, play and sleep. This is not always easy to accomplish, however, as the habit of sleeping in this position may be well established. The position of relative adduction may be maintained by tying gauze loosely around the wrists and fastening it to the bed posts at the foot of the bed, the gauze being kept at such a length that the patient can move the wrists up to approximately the heart level but no further. As he unconsciously moves his arms toward hyperabduction in his sleep the gauze fastened to his wrists becomes taut and the hands drop down to an allowed position. This allows considerable freedom of motion and sleep is not usually affected. Other technics can be used, such as pinning the sleeves of the pajamas to the pajama's trousers or sleeping with the arms inside of the pajamas instead of in the pajama sleeves. These latter technics are, however, somewhat restricting and are not generally as satisfactory as the first. Patients can usually break the habit of sleeping with the arms in hyperabduction in about three to four weeks by using such methods. At first there may be some loss of sleep and restlessness due to the unaccustomed positions. Some patients require sedation until the habit of sleeping with the arms at the sides has become completely established.

If the hyperabduction syndrome is complicated by some underlying vascular or neurologic disease the improved sleeping habits are frequently a valuable asset in the treatment. When the syndrome is associated with anatomic pressures at the shoulder girdle in more common positions as, for examples, the costoclavicular, the cervical rib or the scalenus anticus syndrome, surgical procedures may be necessary to correct these conditions. Surgery is practically never on an emergency basis and the simpler nonsurgical methods should be tried first. When the costoclavicular syndrome occurs together with the hyperabduction syndrome producing a situation so critical that even slight movement occludes the pulse, it

may be necessary to remove the anterior surface of the first rib or to resect the first rib or clavicle.

If the situation happens to be complicated by a scalenus anticus syndrome an attempt at correction may be made by the relatively simple procedure, scalenotomy. When evaluating a short trial with improved posture, due consideration must be given to factors such as residual neuritis, myositis, or trophic changes which might be improved by medical and physical therapy continued over a longer period of time. A few patients have found the discomfort from trying to change their sleeping posture so severe that they elected not to continue attempts to break their habit. The most extreme examples of this occurred in 2 patients who had developed marked trophic changes in their fingers. In such cases the psychologic aspect is of prime importance and requires special attention.

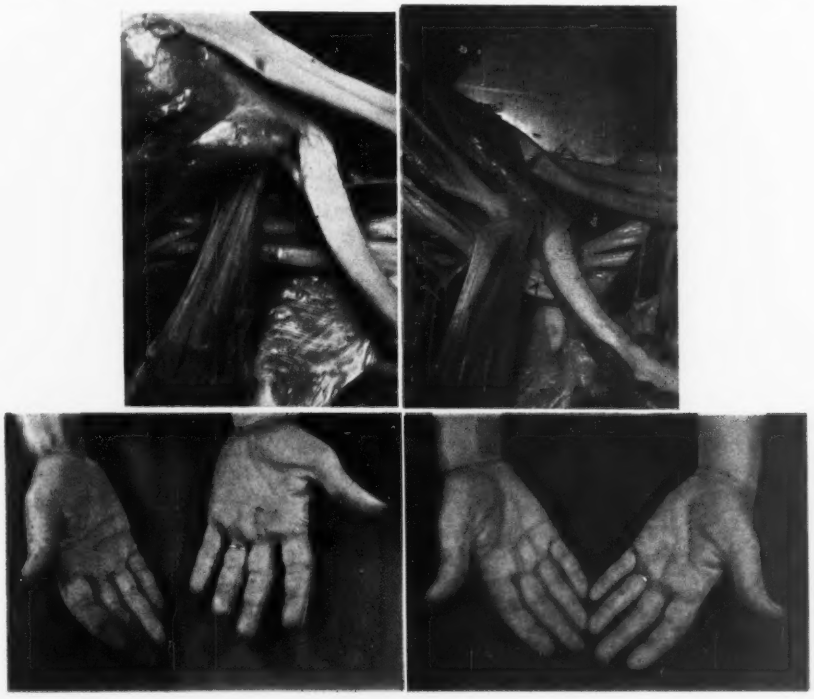

FIG. 1 (*top left*). Dissection of the shoulder girdle. Arm is in adduction. Note adequate space for blood vessels and nerves without compression, stretching or torsion.

FIG. 2 (*top right*). Arm in hyperabduction. Note compression with actual pinching of the subclavian vessels and the brachial plexus between the clavicle and the first rib. (The examiner's finger could not stand the pressure in that space.) Note also the stretching of the axillary artery and the nerves under the coracoid process and behind the pectoralis minor.

FIG. 3 (*bottom left*). Hands of a male patient, age 47, who acquired the habit of sleeping with arms in hyperabduction. Symptoms of numbness, paresthesias and pain developed within three months but the relationship was not recognized. Two months later discoloration of finger tips developed as noted in this picture. Trophic changes were also present at the tips of the same fingers.

FIG. 4 (*bottom right*). Same patient as figure 3, one month later when sleeping position of hyperabduction had been abandoned. No other changes have been made in the patient's regime. Color had returned to normal. All symptoms had disappeared. (*The use of color in these illustrations was made possible by a grant from Wyeth Incorporated to the publication fund of the American Heart Association.*)

Additional suggestions to prevent the recurrence or aggravation of this syndrome include:

(1). Avoidance of excessive strain or injury

involving the arms or shoulder girdle such as bar gymnastics, and heavy high lifting.

(2). Attention on the part of anesthetists, nurses and doctors to the necessity of not maintaining patients' arms in the position of hyperabduction for long periods unless this is absolutely essential.

(3). Arms in airplane splints or casts in this position should be carefully checked for pulses, coldness or discoloration, and complaints from the patient of numbness and other symptoms should be given serious consideration.

(4). Anesthetists should be aware that blood pressure in the arm may be reduced or absent in this position due to occlusion of the artery. Lack of this knowledge may lead to confusion regarding the condition of the patient.[14]

Conclusions

1. In many normal persons the position of hyperabduction of the arms results in occlusion of the subclavian artery and vein and compression of the brachial plexus.

2. If the position of hyperabduction is maintained by such individuals for prolonged periods of time, signs and symptoms may result, some of which may be severe. This is most commonly the result of working requirements or sleeping habits.

3. Raynaud's syndrome may be precipitated or aggravated by the hyperabduction syndrome. When caused by hyperabduction, the avoiding of that position may in some patients result in elimination of Raynaud's syndrome. The relation of these syndromes has not previously been recognized to our knowledge.

4. The hyperabduction syndrome is a more common cause of shoulder girdle and upper extremity symptoms than is generally recognized.

5. The signs and symptoms of the hyperabduction syndrome are in order of frequency: pain, numbness, Raynaud's syndrome, paresthesias, rubor or swelling of the hands, weakness of the hands, and ulceration of the finger tips.

6. Correct diagnosis of syndromes of the shoulder girdle depends on a careful analysis of all the possible causes. The mere observation of poor oscillometric readings in the position of hyperabduction together with occurrence of symptoms in unrelated positions is not sufficient to justify the diagnosis of the hyperabduction syndrome. A causal relationship between the two must be established. This conclusion also should be applied in the diagnosis of the other shoulder girdle syndromes.

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The Effects of Splanchnicectomy on the Blood Pressure in Hypertension

A Controlled Study

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The effect of supradiaphragmatic splanchnicectomy on the blood pressure of 294 hypertensive patients followed for 10 to 18 months after surgery is compared with the effects of nonspecific medical management in a control group of 79 patients similarly studied. The data are presented in simple graphic form. It is concluded that 29 per cent of the hypertensive patients had reductions in blood pressure outside the range of spontaneous variation, that the vascular complications of hypertension decreased the likelihood of a good result, and that extension of the sympathetic ganglionectomy upward appeared to increase the frequency of good results without requiring a two-stage operation or producing significant postoperative orthostatic hypotension.

AN ACCURATE evaluation of the effects of various forms of sympathectomy on the blood pressure in essential hypertension has been complicated in the past by such deficiencies as lack of suitable control studies, variations in number and type of patients selected for surgery, duration of the follow-up observation period, and the methods of obtaining and reporting the changes in blood pressure. The present report of 338 patients studied before and one year after splanchnicectomy and compared with a control group of patients is an attempt at an objective presentation of the effects on the blood pressure to be expected from the procedure of supradiaphragmatic splanchnicectomy and lower dorsal sympathectomy.[1] The data will be presented in a graphic form which lends itself to comparative analysis with the results obtained by more extensive sympathectomies, and finally, our experience concerning the prediction of good and poor results on the basis of preoperative and early postoperative observations will be summarized.

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Dr. Peet died on March 25, 1949.

Methods

Three hundred thirty-eight hypertensive patients underwent splanchnicectomy and 79 similar hypertensives were examined but not operated upon during the time interval January 1, 1947, to June 1, 1948. Information concerning the status of these individuals 10 to 18 months later was obtained by return visit or by replies to questionnaires sent to their physician. No patient over the age of 55 was included in the study, nor, with few exceptions, was any patient accepted whose nonprotein nitrogen exceeded 45 mg. per 100 cc. or whose hypertension was secondary to renal disease or complicated by a recent cerebrovascular accident, myocardial infarction, or congestive heart failure. Seven patients who apparently were on strict low sodium diets at the time of the return visit were excluded from the series, but minor degrees of salt restriction and the use of sedatives did not serve to eliminate the patient from the study. The operation consisted of the bilateral removal at one stage of the greater and lesser splanchnic nerves and sympathetic ganglions D-12 and above.[1] The usual upper limit of removal was D-8 but in a number of instances it was possible to remove two or more ganglions above this point. All operations were done by members of the Department of Neurosurgery.

The blood pressure was determined in the following manner: "Casual" blood pressures represented the average of three consecutive determinations in the recumbent position in the right arm, obtained by the physician shortly after seeing the patient in one of the clinics of the University Hospital or by a specially trained technician when the patient was examined in the Cardiovascular Unit,

where this study was carried out for the most part. The resting blood pressure was obtained after 30 minutes rest alone in a quiet room. The cold pressor test and the tetraethylammonium tests were performed as described elsewhere.[2,3]

Observations

1. *Variation in Blood Pressure in the "Control" Group*

Of 79 patients selected because their initial examination was sufficiently complete and their studies indicated they would have been acceptable for surgery, 10 died and 10 could not be followed up in the one year interval. The blood pressure changes of the remainder are presented in figure 1. A reduction in the diastolic pressure exceeding 20 mm. Hg occurred in only one patient who returned in congestive heart failure. The systolic pressure varied between an increase of 40 and a decrease of 30 mm. Hg in 96 per cent of the cases studied.

We recognize that these "control" patients are in a sense selected, since in our institution splanchnicectomy is commonly recommended. However, all of these patients were suitable candidates for splanchnicectomy, and 43 had actually been accepted by the Neurosurgery Service for operation. While a certain factor of selection applied, in most cases financial, administrative, or reasons other than those related to the severity of the disease kept them from surgery. This is further borne out by a study of the blood pressure distribution and frequency of retinal, cardiac, and cerebral changes in the "control" series, and the mortality rates over the year interval which were very nearly comparable in the two groups of patients. For this reason we believe that the experience with the patients who were not operated upon serves as a dependable background for judging the effects of splanchnicectomy on the blood pressure.

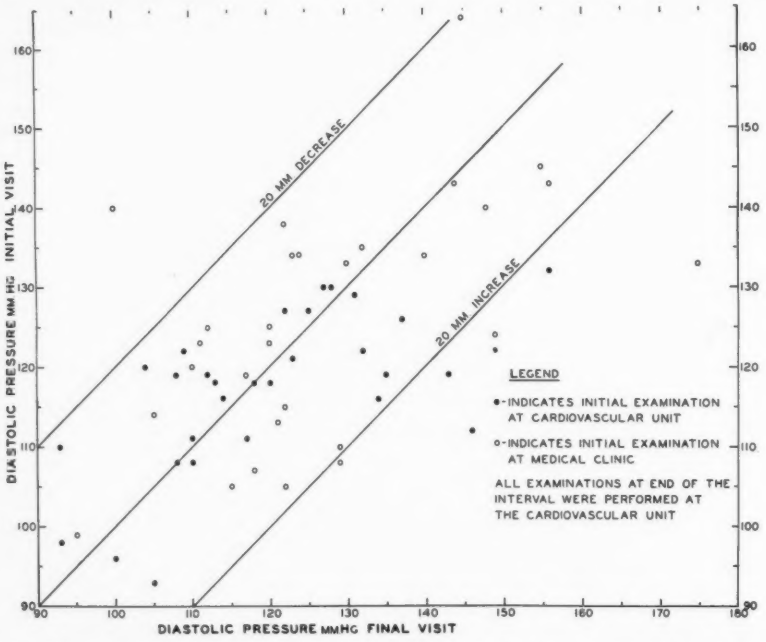

Fig. 1. Effect of nonoperative treatment on the diastolic blood pressure in 59 patients, who received no significant medical or surgical treatment during the interval, re-examined 10 to 18 months after initial visit to Hospital. The graph is so constructed that reductions of more than 20 mm. in diastolic pressure are represented by points above the upper diagonal and increases of more than 20 mm. by points below the lower diagonal. It will be seen that spontaneous reductions in diastolic pressure exceeding 20 mm. over the year interval were rare under the conditions of this study.

2. *Analysis of the Preoperative and Postoperative Blood Pressure Data*

Three hundred thirty-eight patients were operated upon during the period of the study. It was impossible to secure follow-up information one year later on 13 of these patients. Thirty-one had died in the interval. Ten patients died during the operation or a few days thereafter which gave an operative mortality of 3 per cent. Twenty-one patients died during the year following the operation. Thus, it was impossible to secure blood pressure data on 44 of the 338 patients one year postoperatively.

Information concerning the remainder is available. One hundred fifty-four patients lived within the 200 mile radius of Ann Arbor and were re-examined at the Cardiovascular Unit. Figure 2 presents the findings on these patients. One hundred forty patients came to Ann Arbor from outside the 200 mile zone and were largely private patients of one of us (M. M. P.). Information concerning the postoperative blood pressure status of these patients was obtained by correspondence with the patients' private physicians and the findings are presented in figure 3. The median reduction in diastolic blood pressure in the patients re-examined by the home physician was 20 mm. Hg (from 126 to 106) while the reduction recorded in the patients re-examined at the Cardiovascular Unit was 13 mm. Hg (from 127 to 114). For purposes of simplicity in the subsequent analyses the two series of patients are grouped together.

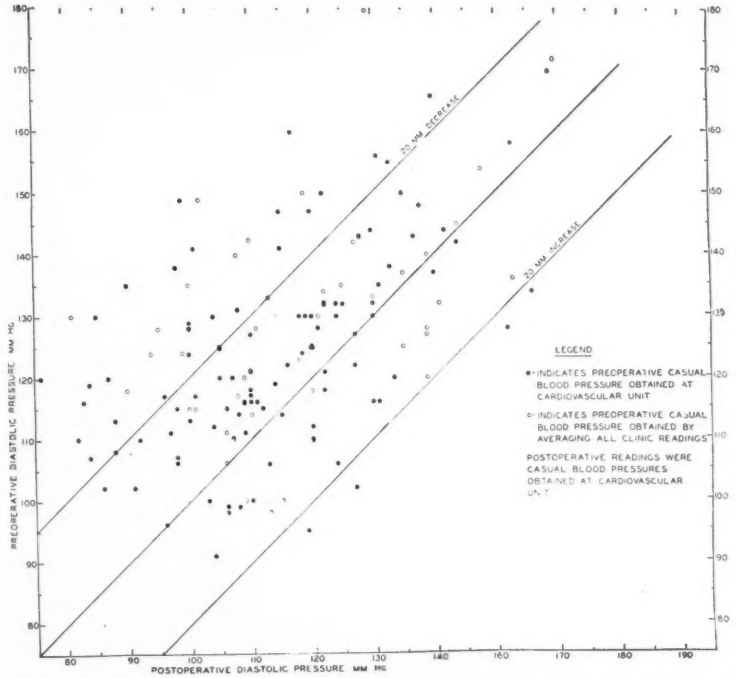
20 MM. DECREASE
20 MM. INCREASE
LEGEND
INDICATES PREOPERATIVE CASUAL BLOOD PRESSURE OBTAINED AT CARDIOVASCULAR UNIT
INDICATES PREOPERATIVE CASUAL BLOOD PRESSURE OBTAINED BY AVERAGING ALL CLINIC READINGS
POSTOPERATIVE READINGS WERE CASUAL BLOOD PRESSURES OBTAINED AT CARDIOVASCULAR UNIT
PREOPERATIVE DIASTOLIC PRESSURE MM HG
POSTOPERATIVE DIASTOLIC PRESSURE MM HG

FIG. 2. Changes in diastolic blood pressure in 154 patients re-examined at University Hospital one year after splanchnicectomy.

Ninety-eight of the surviving patients had diastolic blood pressure reductions exceeding 20 mm. Hg (that is, above the upper diagonal line in figs. 2 and 3). These reductions were outside the limits obtained in all but one of the 59 control patients (fig. 1). This represents 33 per cent of the survivors, or 29 per cent of the entire series. Figures 2 and 3 also demonstrate that the reductions were of sufficient magnitude to bring the diastolic pressure to below

90 mm. Hg in 26 patients, or 7 per cent of the entire series.

Significant reductions occurred more frequently in patients with high initial blood pressures. Of 73 patients whose initial diastolic pressures were between 131 and 145, 29, or 40 per cent, were reduced by more than 20 mm. Hg, and 4 fell to below 90 mm. Hg (figs. 2 and 3). Of 13 control subjects with comparable

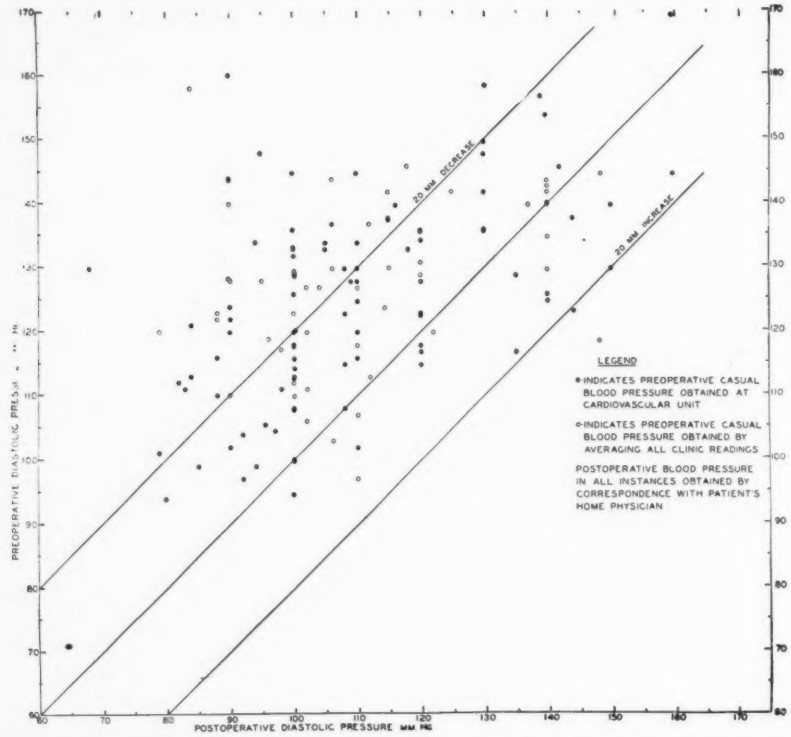
20 MM. DECREASE
20 MM. INCREASE
LEGEND
INDICATES PREOPERATIVE CASUAL BLOOD PRESSURE OBTAINED AT CARDIOVASCULAR UNIT
INDICATES PREOPERATIVE CASUAL BLOOD PRESSURE OBTAINED BY AVERAGING ALL CLINIC READINGS
POSTOPERATIVE BLOOD PRESSURE IN ALL INSTANCES OBTAINED BY CORRESPONDENCE WITH PATIENT'S HOME PHYSICIAN
POSTOPERATIVE DIASTOLIC PRESSURE MM HG

FIG. 3. Changes in diastolic blood pressure in 140 patients re-examined, one year after splanchnicectomy, by home physician.

elevations of blood pressure, only one showed a decline exceeding 20 mm. Hg diastolic; she had gone into congestive failure and a failing cardiac output may have accounted in part for the reduction.

Patients with initial diastolic blood pressures below 110 mm. Hg did not frequently experience significant reductions in pressure after surgery. Of 41 such patients only 6 (15 per cent) had postoperative blood pressures below 90 mm. Hg, and 2 alone had reductions exceeding 20 mm. Hg. Changes of similar magnitude did not occur in any of 10 control patients with initial blood pressures in the same range. Because of the experience with the control group, we have not listed blood pressure reductions of less than 20 mm. Hg diastolic as "significant." However, it will be noted from figures 2 and 3 that there is a general tendency toward reductions in blood pressure in most of the patients operated upon, so that a median reduction of 16 mm. Hg (126 to 110) occurred. This is to be compared with a median alteration of 0 (122 to 122 mm. Hg) in the control group.

Because of the greater number of patients who could be studied, we made comparisons of the "casual" readings, but analyses of the blood pressures obtained after 30 minutes rest in a quiet room showed the same degree of improvement. Twenty-six per cent of a series of 88 patients so studied showed reductions of more

than 20 mm. Hg in the resting blood pressure at the one year postoperative examination.

The systolic pressure fell with equal frequency. Ninety-five patients, or 28 per cent of the entire series, had systolic pressure reductions exceeding 30 mm. Hg, which is outside the range of spontaneous variations in the control series.

3. *Type of Patient Most Likely to Obtain a Good Result*

In order to identify any factors of prognostic value, 31 individuals who died in the follow-up year and 40 who had experienced less than a 10 mm. reduction in diastolic pressure were contrasted with 60 patients who had had the most significant reductions in pressure compared with their average blood pressure over two or more months before operation. Patients with diastolic blood pressures of less than 110 mm. Hg and those with malignant hypertension were excluded from both series. A detailed list of these patients with the frequency and range of blood pressure determination and with a comparison of the characteristics of the "good" and "poor" result group has been reported elsewhere,[4] but may be summarized at this point. Age distribution, known duration of hypertensive disease and preoperative response to tests of vasolability (cold pressure rise, tetraethylammonium decrease, decline between casual and resting levels) were practically identical in the two groups. Females were found with slightly greater frequency in the good result group. Patients with wide pulse pressures according to Smithwick's classification[5] were more commonly found in the poor result category, but narrow pulse pressures did not occur more frequently in the cases who were to have a good postoperative outcome.

In respect to two characteristics, however, the two groups differed significantly. Patients with higher initial blood pressures tended to fall more frequently in the "good result" category, while those with lower initial pressures were more apt to have a "poor" postoperative response. The second point of significant difference lay in the more frequent occurrence of the vascular complications of hypertension in the patients who had poor postoperative results. This might have been anticipated, since among the poor results were included 31 who subsequently died. The problem was therefore studied from a different viewpoint by examining the postoperative outcome of patients with various types of hypertensive complications and comparing them with the control material. This data is presented in table 1. It will be seen that a major complication of hypertension reduces the likelihood of a postoperative blood pressure reduction, but that such improvement occurs more frequently than would be expected from the course of the disease in the untreated hypertensive patient.

As would be expected, patients with malignant hypertension did far worse than those with uncomplicated essential hypertension. We were persuaded to operate on 7 cases who had marked azotemia in addition to papilledema. Only 2 survived one year and only 1 of these had a reduction in pressure. Almost one-half of the 18 patients with papilledema whose nonprotein nitrogen could be kept below 45 mg. per 100 cc. by medical management survived the one year interval, and a number of these reported symptomatic improvement and disappearance of papilledema. One-fourth of the survivors had substantial reductions of blood pressure as well. Control material from this clinic is not available to follow the natural course of this form of the disease since we have believed that these desperately ill patients deserve the chance of surgical intervention.

4. *Prediction of Ultimate Course from Early Postoperative Observation*

Certain patients living near Ann Arbor have been re-examined repeatedly up to one year since operation, in an attempt to learn at what time the blood pressure becomes stabilized at the level to be expected one year after operation. Only 3 to 7 per cent of patients whose diastolic pressure nine days, three months, or six months after operation had risen to within 20 mm. of their preoperative level could be classified as "good results" at the end of one year. A reduction in the early postoperative blood pressure, however, by no means guaranteed a favorable result. From table 2 it will

TABLE 1.—*Follow-up Status of Splanchnicectomized and Control Patients with and without Certain Vascular Complications of Hypertension*

Initial Status of Patients	Total Cases	Dead	Survivors		
				B.P. Reduced	
	No.	No.	No.	No.	% Entire Series
I. Hypertension uncomplicated					
Surgically treated	127	4	123	43	34
Control	25	0		0	
II. Hypertension without papilledema					
(a) ECG abnormal					
Surgically treated	130	19	111	42	32
Control	25	7	18	1	4
(b) Heart enlarged					
Surgically treated	60	15	45	12	20
Control	10	5	5	1	10
(c) Focal encephalopathy or stroke					
Surgically treated	18	2	16	2	11
Control	0	0	0	0	0
III. Hypertension with papilledema					
NPN over 45 mg. per 100 cc. Surgically treated	7	5	2	1	14
NPN under 45 mg. per 100 cc. Surgically treated	18	10	8	2	11

Diastolic blood pressure initially exceeded 110 mm. in all patients in this table. Reduction was defined as a fall of 20 mm. or more in diastolic blood pressure on follow-up examination. ECG abnormalities included inversion of T_1, T_2, axis deviations or other abnormalities as interpreted through the courtesy of Dr. Frank N. Wilson and Dr. Franklin Johnston of the Heart Station of the University Hospital. Cardiac enargement was defined as an increase in transverse diameter of the heart by x-ray of 15 per cent or more above normal standards for height and weight.[18] Cerebrovascular complications had occurred within the year prior to the initial examination at the University Hospital.

Patients with papilledema were treated separately, although other hypertensive complications were also present. No suitable control material was available for purpose of comparison.

be seen that the percentage of "good" results falls off steadily as the observation period lengthens. It might be supposed that if such a decline continued the number of good results at two years would be negligible. Fortunately such is not the case. A previous study of 30 "good result" patients who have been followed for more than two years indicates that only one has shown a significant increase in the blood pressure in the second postoperative year.[4] It appears, therefore, that at the end of one year the blood pressure had become reasonably stabilized and it is then possible to estimate the frequency of good results.

5. *Extent of Denervation as a Factor in Postoperative Result*

According to the operative note, removal of D-12 bilaterally was accomplished in every patient. L-1 was occasionally removed but so rarely as to preclude any statistical analysis of the results. The upper limit of ganglionectomy, however, varied widely with the difficulty of the operation and the skill of the operator. Fifty-four cases were reported to have had bilateral excision including ganglions D-6 or above: 27, or 50 per cent, of these patients had significant reductions in blood pressure one year later. On the other hand, it was impossible to remove any ganglions above D-9 in 43 instances: 9, or 21 per cent, of these patients experienced a good postoperative result. Examination of the operative notes in the 60 cases of "certainly good" results listed in our previous report[4] revealed that 43 per cent had had bilateral removal of ganglions D-6 to D-12 compared with 21 per cent of the "poor" result cases.

TABLE 2.—*Reduction in Blood Pressure at Various Time Intervals after Surgery*

No. Cases Observed	% Cases with Reduction of 20 mm. or more in Postoperative Casual Diastolic Blood Pressure at			
	9 Days	3 Months	6 Months	12 Months
294	67	—	—	32
57	—	53	—	30
186	—	—	44	28

6. *Characteristics of the Postoperative State*

(a) *Blood Pressure.* The operation reduced only slightly the spontaneous or induced fluctuations so characteristic of the disease. The median response of the diastolic blood pressure to the cold pressor stimulus was plus 20 mm. Hg preoperatively and plus 20 mm. Hg postoperatively in 65 patients so studied. The "good result" patients still showed considerable vascular lability. They had a median response of plus 17 mm. Hg.

The response of the postoperative patient to tetraethylammonium chloride was unchanged. Reductions of about 20 per cent in the diastolic blood pressure continued to occur even in the "good result" cases. In an attempt to determine whether significant vasomotor tone persisted in the thoracoabdominal area after splanchnicectomy, we tested the tetraethylammonium responses of a number of patients in whom the legs and one arm had been previously excluded from the circulation by tourniquets inflated for three minutes to 40 mm. above arterial pressure. While the occlusion was continued, 300 mg. of tetraethylammonium was injected. A reduction in blood pressure continued to occur, particularly in those patients whose hypertension had not been materially reduced by splanchnicectomy. This observation suggests the persistence of significant vasomotor tone to the thoracoabdominal area in these individuals.

Orthostatic hypotension was rarely observed two weeks or more after surgery. The blood pressure was measured in the recumbent position and during three minutes or more of motionless standing in the first 122 patients examined at 3, 6 or 12 months following operation. Reductions were observed so infrequently that the procedure was thereafter discontinued.

(b) *Postoperative Disability and Symptomatic Improvement.* As previously mentioned, patients were discharged from the hospital on about the tenth day following surgery. They were usually able to return to work in two to three months' time. Orthostatic syncope was not reported. Postoperative back pain was the chief disabling symptom referable to surgery. It was mentioned as an occasional annoyance in 35 per cent of patients six months after operation, but in 9 per cent of individuals it was sufficiently severe to interfere to some extent with the patients' normal activity or occupation. At the one year check-up examination this symptom was rarely disabling.

Relief from the symptoms of hypertension was frequently gratifying and out of proportion to the improvement in the blood pressure. Of a series of 97 patients who had had headaches of varying severity preoperatively, 5 were unimproved, 43 improved, and 49 had complete relief one year following surgery. Dizziness, nervousness, and irritability were likewise reduced to a significant extent. It was less certain that dyspnea, blurring of vision, or hypertensive encephalopathy was improved, owing to the difficulty of defining these symptoms accurately, or of establishing their frequency of occurrence before operation, but it was our clinical impression that improvement was often gratifying. Angina pectoris was not frequently relieved. In addition to this symptomatic relief, improvement in electrocardiogram and in heart size by teleroentgenogram was encountered. Such improvement occurred witb greatest regularity in patients whose blood pressure was reduced significantly. It also occurred in occasional patients who had little reductions in pressure, but not at all in the control group. Ninety-five per cent of the patients who were asked whether they were glad they had had the operation replied in the affirmative. Even allowing for individual optimism, this is a gratifying response.

Discussion

1. *Evaluation of Various Forms of Sympathectomy for Hypertension*

This study indicates that supradiaphragmatic splanchnicectomy will lower the blood pressure significantly in about one third of hypertensive patients, but will rarely be "curative." Since the operation can be completed in one stage with minimal postoperative disability, it is worthwhile to inquire whether the results of the more extensive two stage procedures justify the added hospitalization and the postoperative orthostatic hypotension. Table 3 has been constructed for this purpose. While such comparison cannot be very ac-

curate, owing to the different indications for surgery, to the varying follow-up intervals, and to the different criteria of improvement used by various clinics, it would appear that extension of sympathectomy improves the postoperative results as far as the blood pressure is concerned. Our observations that removal of ganglions D-6 and above improved the results are in accord with this finding and suggest that a wider thoracic ganglionectomy may be as useful as extending the operation to include the lumbar ganglions.

TABLE 3.—*Reported Effect of Various Forms of Sympathectomy on the Blood Pressure in Hypertension*

Authors	Extent of Ganglionectomy	No. Cases Reported	Follow-up (years)	"Good" Results	Definition of "Good" result
				%	
Grimson[6]	Stellate through L-1 or L-2	113	1–8	66	Comparable pre- and postoperative data for each patient not presented. Median reduction in diastolic readings of all patients exceeded 20 mm. Hg at 1 year and appeared sustained in subsequent years. Deaths included.
Evans and Bartels[7]	D-3 or 4 through L-1	173	½–3	47	Casual diastolic blood pressure fell more than 20 mm. and to less than 120 mm. in "good result" cases.
Smithwick[8]	D-8 through L-1	439	1–5	37	Postoperative blood pressure fell 20 mm. or more below resting preoperative diastolic blood pressure. Deaths included.
Hammarstrom[9]	D-8 through D-12 D-8 through L-1 or 2	25 55	½–6½	42 59	Mean of 24 hourly diastolic blood pressure readings in hospital reduced more than 25 mm. Deaths included. More extensive sympathectomy improved results in males particularly.
Peet, Woods, Braden[10]	D-8, 9 or 10 through D-12	202	9–18 mos.	18–44	Casual diastolic blood pressure declined more than 25 mm. in 18%, more than 15 mm. in 44%, deaths included.
Present Series	D-6, 7, 8 or 9 through D-12 (D-6 through D-12)	338 (54)	10–16 mos.	29 (50)	Casual diastolic blood pressure reduced more than 20 mm. Hg. Deaths included.

The effects of splanchnicectomy are as likely to persist as are those of the other surgical

procedures. Patients in our series who had had a good result at one year maintained their improvement in subsequent years almost without exception. This conforms with the opinion of the majority of observers[4, 6, 10] but Evelyn and co-workers[11] pointed out that recurrences were frequent between the first and fifth year after lumbodorsal sympathectomy, so that in their experience the ultimate percentage of "good" results* fell to only 21 per cent.

2. *Mode of Action of Splanchnicectomy in Hypertension*

The fact that the blood pressure reduction, if it is to occur at all, is observed in the early postoperative period implies that the operation removes immediately an important area of increased vascular resistance. This could be accomplished indirectly by altering the output of, or vascular response to, adrenal or renal secretions, but it might also be the result of decreasing the splanchnic vascular resistance by interrupting splanchnic vasomotor tone.

A postoperative return to hypertensive levels could occur by means of (1) compensatory vasoconstriction in nondenervated areas, (2) by restoration of neural control of the splanchnic bed, and (3) by recovery of intrinsic vascular tonus within the denervated vascular bed.

While increased vasoconstrictor tone may occasionally develop in the undenervated areas of the body following splanchnicectomy, it appears unlikely that such compensatory vasconstriction is a common cause for return to hypertensive levels, since blockade of vasomotor tone by tetraethylammonium in such persons does not produce excessive increases in blood flow to the extremities.[12] Restoration of neural control to the splanchnic area via a ganglionic pathway may be a factor in operative failures. This hypothesis is supported by the experiment wherein tetraethylammonium reduced blood pressure in the splanchnicectomized subject after exclusion of the extremities from the circulation by arterial tourniquets, and it is also implied by the studies of Ray and Console[13] who showed that sweat activity returned to the denervated area but could again be interrupted by ganglionic blocking agents. Such vasomotor tone could reach the splanchnic vessels via alternate neural pathways or by regrowth of sectioned postganglionic fibers. In either event a wider sympathetic ganglionectomy might reduce the chances for restoration of such neural control, and this might explain the apparent improvement in postoperative results achieved by upward extension of the sympathectomy. Finally, recovery of intrinsic tonus in the denervated splanchnic bed may be responsible for the late return of hypertension after splanchnicectomy. Observations following sympathectomy of the extremities indicates that this recovery proceeds rapidly in the first few weeks, and that blood flow finally stabilizes at or above preoperative levels in two to three months postoperatively.[14] It is possible that we are dealing with such a situation after splanchnicectomy. Wilkins' splanchnic blood flow measurements have demonstrated that a progressive reduction in blood flow occurs after operation, although he could not relate these changes to the success or failure of surgery.[15]

It will be noted that the above hypothesis does not assume that certain hypertensive patients are benefited by sympathectomy simply because they have excessive neurogenic vasomotor tone. Rather, it assumes that all patients with hypertension (and probably normotensive patients as well) have a certain normal neurogenic support to their peripheral vascular resistance. This accounts for the fact that spinal anesthesia or autonomic blocking agents will lower the blood pressure of most patients with hypertension,[2,16] that such procedures will even lower the blood pressure of dogs with Goldblatt kidneys[17] and that these reductions occur regardless of the degree of arteriosclerosis or of apparent renal participation in the hypertension. In this view, sympathectomy will have a tendency to reduce the blood pressure in all patients with elevated blood pressure, regardless of the cause or duration of the disease. That this occurs is demonstrated by the slight lowering of almost all postoperative blood pressures shown in figures 2 and 3. Furthermore, the frequency of significant reductions in blood

* Criteria not stated, but it would appear that 20 mm. reduction in median diastolic blood pressure would qualify.

pressure would depend to some extent on the completeness of the initial removal of neurogenic support but to a greater extent on the degree and magnitude of compensating influences which develop in the postoperative period. Since these influences are essentially unpredictable by any preoperative maneuver, it would explain our failure to find any method of preselecting patients for splanchnicectomy. If we assume, on the other hand, that certain hypertensive patients are "neurogenic" in the sense that their peripheral vascular resistance is elevated by excessive vasoconstrictor tone, it becomes much more difficult to explain the observations discussed above.

3. *Indications for Surgery*

No preoperative test was found of predictive value. However, on the basis of experiences reported in this paper, certain trends were observed. Patients with high diastolic blood pressures were more likely to experience improvement, and it was therefore usually recommended for this group. Individuals with the vascular complications of hypertension (previous cerebrovascular accident, cardiac enlargement, papilledema) experienced blood pressure reductions less frequently (11 to 20 per cent) but since they carry a more serious prognosis[19] surgical therapy was usually advised for this group. Finally, relief of certain hypertensive symptoms, particularly headache, was so frequent as to be an important consideration in recommending this form of treatment.

We found that only 15 per cent of patients with initial diastolic pressures below 110 mm. Hg fell below 90 mm. Hg after sympathectomy. Conservative therapy was therefore advised for this group. Patients with an elevated nonprotein nitrogen due to poor renal function were found to have such a high mortality rate and such poor postoperative results as not to justify surgery.

If these indications are kept in mind, and it is recognized that sympathectomy is more apt to be palliative than curative in hypertension, we believe that supradiaphragmatic splanchnicectomy has a definite place in the management of the hypertensive patient.

Summary and Conclusions

1. Three hundred thirty-eight hypertensive patients were followed 10 to 18 months after supradiaphragmatic splanchnicectomy and 79 similar patients who did not undergo surgery were followed for a comparable period to serve as control subjects.

2. Only one of the controls showed a reduction of greater than 20 mm. in the diastolic pressure, while 29 per cent of the patients who were operated upon showed such a reduction in blood pressure, and 7 per cent showed a return to normotensive levels.

3. The preoperative data on 60 patients with the most marked reductions in blood pressure were compared with 71 who had had poorest results from surgery. No significant differences in the preoperative characteristics of the two groups could be established. Patients with diastolic blood pressure below 110 mm. or hypertensive vascular complications (cardiac enlargement, cerebrovascular accidents or papilledema) were less likely to experience significant blood pressure reductions following surgery.

4. If the blood pressure returned to preoperative levels by the ninth postoperative day, a negligible number of patients showed significant reduction one year postoperatively. On the other hand, blood pressure reductions in the early postoperative period often returned to hypertensive levels at a later date, so that an ultimate good result was not assured until one year had elapsed. Patients who had had good results at one year did not experience further elevation in the second postoperative year.

5. Patients in whom the denervation had been extended upward from D-12 to include D-6 or above bilaterally had a better postoperative result (50 per cent) than those in whom the conventional ganglionectomy (D-8 to D-12) had been performed.

6. The magnitude of the response to cold pressor tests was not reduced by operation. Orthostatic hypotension was not encountered and general postoperative disability was minimal after this type of sympathectomy, while symptomatic relief was as frequent as reported for more extensive operations.

7. While blood pressure reductions were perhaps not as common as those which are reported

to follow other types of sympathetic surgery, we believe that this less radical operation has a real place in the routine treatment of established hypertensive disease which does not respond to medical management.

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Further Studies of the Cerebral Chemoreceptor Buffers as Influenced by Vasoconstrictor and Vasodilator Drugs and Veratrum Viride

By Robert D. Taylor, M.D., and Irvine H. Page, M.D.

These experiments extend our studies on the newly described cerebral chemoreceptors to show that most pressor drugs cause peripheral hypotension when perfused through the brain of the animal isolated except for nervous connections with its body. Depressor drugs usually act oppositely and cause hypertension. The cerebral chemoreceptors thus seem to act as a buffer mechanism. The receptors may be inactivated to some drugs without blocking the neurogenic hypertension response elicited by cerebral ischemia. Veratrum viride is shown to be such a drug. Besides initiating the von Bezold reflex, veratrum lowers blood pressure by direct central action.

WE HAVE described[1] a method which effectively isolated the circulation of the brain from that of the body of dogs and yet preserved nervous connections through the spinal cord. Perfusion of the isolated head depended upon a donor animal or a pump. With this preparation we demonstrated peripheral action, mediated through sympathetic nerves, of vasomotor drugs acting solely upon the brain. Adrenaline and noradrenaline were shown to be potent vasodilators of the peripheral vascular tree independent of the carotid sinuses and vagus nerves, since dilatation was elicited after their inactivation. Hence, it was assumed there were chemoreceptors in the brain which served as part of the buffer system against blood pressure changes of chemical origin.

This communication deals with the effects on peripheral circulation of other substances when perfused through the brain that are pressor or depressor in the intact animal.

Method

Two mongrel dogs, anesthetized with pentobarbital, were used in each of fifty-two experiments. The circulation of the head of the "recipient" animal was separated from the body as we have described.[1] The carotid sinuses were denervated by cutting the nerves of Hering and stripping the adventitia from the bifurcation of the carotid arteries. Denervation was demonstrated by clamping the carotid arteries below the sinuses. If no change in peripheral blood pressure was observed the reflex was considered abolished. The vagus nerves were cut. Unless otherwise specified, the buffer nerves were destroyed in all experiments. The cardiac ends of a jugular vein and carotid artery of the donor dog were connected by plastic tubing with the ends of similar vessels leading to and from the brain of the recipient animal for perfusion of the isolated central nervous system. Drugs to be tested were usually injected into a two way stopcock inserted into the arterial side of the perfusion circuit. In experiments exploring the action of veratrum viride (Veriloid*), some injections were made intravenously into the recipient dog's body. Barium chloride (9.0 mg.), nicotine (0.15 mg.), histamine (0.1 mg.), Mecholyl (acetyl-β-methyl choline, 0.1 to 0.25 mg.), and a purified veratrum viride preparation (Veriloid, 0.04 mg. to 0.1 mg.) were tested. The volume of each injection was 1.0 cc. Experiments required three to five hours preparation and lasted three to six hours.

Blood pressure of the donor dog and the body of the recipient animal were recorded on two smoked drums by a mercury manometer, from a femoral artery. The tubing leading from the artery to the manometer contained 1:1000 dilution of heparin in normal saline. Heparin, 4 mg. per Kg. of body weight, was given to the donor dog to prevent clotting in the perfusion circuit.

Results

Pressor Drugs

A. Barium chloride caused respirations of the recipient to be deep and rapid for one to two minutes. Blood pressure in the body of the

From the Research Division of the Cleveland Clinic Foundation and the Frank E. Bunts Educational Institute Cleveland, Ohio

* Veriloid was kindly supplied by Dr. Philip Bates, President of the Riker Chemical Company, Los Angeles, Calif.

TABLE 1.—*Effects on the Peripheral Blood Pressure of Pressor Drugs Acting upon Cerebral Chemoreceptors*

Experiment	Barium Chloride (9.0 mg.)				Experiment	Nicotine (0.15 mg.)			
	Recipient Dog Blood Pressure		Donor Dog Blood Pressure			Recipient Dog Blood Pressure		Donor Dog Blood Pressure	
	Control	Pressure Change	Control	Pressure Change		Control	Pressure Change	Control	Pressure Change
	mm. Hg		*mm. Hg*			*mm. Hg*		*mm. Hg*	
1	138	−18	124	+12	1	102	−36	148	+112
	130	−24	126	+10					
2	142	−98	134	+10	2	158	−98	136	+10
	132	−30	132	+4					
3	130	−30	134	+12	3	130	−16	172	+12
4	100	−36	146	+4	4	130	−16	176	+50
	98	−32	150	+28					
5	140	−18	110	+38	5	148	−24	150	+18
	132	−24	112	+24					
6	118	−30	118	+10					
7	84	−8	120	+22					
8	96	−18	132	+12					
9	110	−18	140	+22					
10	86	+22	126	+6					
	98	+48	130	+0					

TABLE 2.—*Effects on the Peripheral Blood Pressure of Depressor Drugs Acting upon Cerebral Chemoreceptors*

Experiment	Histamine (0.1 mg.)				Experiment	Mecholyl (0.25 mg.)			
	Recipient Dog Blood Pressure		Donor Dog Blood Pressure			Recipient Dog Blood Pressure		Donor Dog Blood Pressure	
	Control	Pressure Change	Control	Pressure Change		Control	Pressure Change	Control	Pressure Change
	mm. Hg		*mm. Hg*			*mm. Hg*		*mm. Hg*	
1	142	+18	146	−52	1	122	+30	94	−60
	122	+14	160	−46					
	134	+20	158	−70					
2	104	+26	168	−76	2	114	+40	110	−38
	84	+96	170	−76					
	72	+128	164	−34					
3	64	+15	136	−40	3	64	+140	150	−40
	68	+22	130	−28					
4	88	+42	126	−36	4	96	+128	144	−62
	80	+54	128	−30		152	+132	146	−54
5	112	+18	140	−20	5	90	+78	140	−80
	120	+30	136	−12		108	+28	140	−54
						114	+32	150	−46
6	132	−12 & +20	138	−26	6	100	+78	148	−52
	140	−10 & +30	140	−22		156	+78	140	−60
7	130	−48 & +74	162	−52	7	70	+208	144	−76
	180	−18 & +40	158	−44		74	+176	148	−80
						66	+98	130	−50
8	130	−8 & +14	128	−24	8	138	+66	144	−32
	142	−14 & +8	130	−16		90	+40	144	−24
9	120	−36 & +14	128	−66	9	64	+154	106	−52
	118	−24 & +26	130	−40		74	+106	118	−38
10	138	−30	142	−40	10	140	+68	156	−96
	124	−22	150	−42					

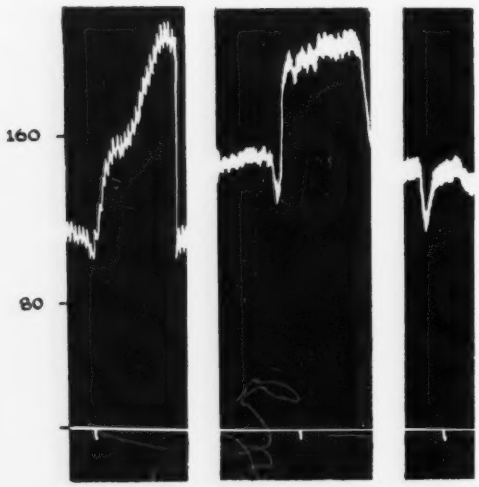

FIG. 1. Types of peripheral blood pressure response to centrally acting histamine. *Left:* Seventy per cent of animals had pure pressor responses to centrally acting histamine. *Center:* Thirty per cent had a diaphasic response. *Right:* An occasional animal showed only a fall of peripheral pressure.

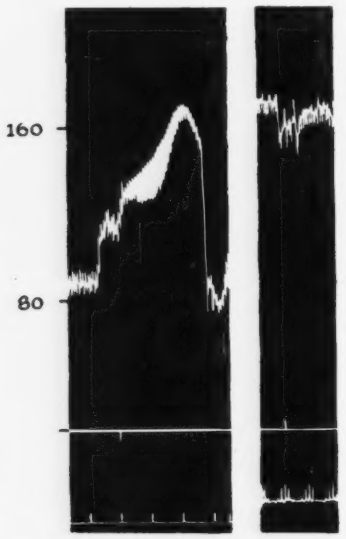

FIG. 2.—Blood pressure change in recipient and donor dogs after intra-arterial injection of Mecholyl. *Left:* Rise of peripheral blood pressure of recipient dog after intra-arterial injection of Mecholyl 0.1 mg. *Right:* Mecholyl was so diluted in donor dog's blood that only a slight fall of blood pressure was observed.

recipient dog almost always fell 8 to 98 mm. Hg, whether or not it changed in the donor, (table 1). Probably because of dilution in the donor's blood and the rate of venous return, the pressor response of the donor dog was often slight or absent.

In one of ten experiments barium chloride

TABLE 3.—*Effects of Veratrum on Peripheral Blood Pressure*

A. In recipient dog's body with vagi intact

Control	Degree of Change
mm. Hg	*mm. Hg*
1. 104	−24
2. 138	−50
3. 80	−60
4. 96	−20
5. 110	−18

B. In recipient dog's body with vagi cut

1. 100	0
2. 138	0
3. 84	0
4. 130*	0
5. 88	0
6. 92	0
7. 82	0

C. In isolated brain of recipient dog†

1. 120	−22
2. 90	−40
3. 130	−42
4. 100	−36
5. 136	−44

* Total 3.0 mg. Veriloid given intravenously.

† After a single injection of 0.1 mg. of Veriloid blood pressure continued at reduced level indefinitely and chemoreceptors were not responsive to other drugs tested.

caused a rise of blood pressure of the recipient's body; responses to other drugs were usual.

B. Nicotine caused intense respiratory stimulation in the recipient dog lasting two to four minutes after each injection in five experiments. The peripheral blood pressure of the recipient animal was reduced 15 to 98 mm. Hg (table 1). As with other drugs tested, the blood pressure rise of the donor dog was irregular due chiefly to the varied rate of return circulation and the size of the animal. It bore no relationship, how-

ever, to the degree of response in the body of the recipient dog.

Vasodilator Drugs

A. Histamine. One-tenth mg. of histamine phosphate usually caused a sharp rise in the peripheral blood pressure of the recipient dog when acting centrally (14 to 128 mm. Hg). This was not as regular as the response to adrenaline, noradrenaline, or Mecholyl. In 1 out of 10 cases, intra-arterial injection caused blood pressure of the recipient's body to fall and in about one-third the response was diphasic with a slight fall preceding the rise (table 2). The type of responses observed are shown in figure 1.

Late in the course of some experiments, histamine, which had caused a typical pressor response, exhibited no effect, possibly because of exhaustion of the mechanism or the onset of tachyphylaxis. It is of interest that under these conditions ischemia induced by clamping the artery perfusing the brain, caused a sharp rise of blood pressure in the recipient's body (100 to 190 mm. Hg).

B. Mecholyl (acetyl-β-methyl choline) always elevated pressure when circulated through the brain by intra-arterial injection. The response was often as much as 150 mm. Hg, and ranged from 30 to 208 mm. Hg. As shown in table 2 and figure 2, this response bore no relationship to the degree of pressure fall in the donor dog.

C. Veratrum Viride (*Veriloid*). In addition to observations of the central action of veratrum, experiments were arranged to elicit the von Bezold reflex. This reflex has been suggested as a partial explanation for the hypotensive effects of veratrum in intact animals. The reflex is due to stimulation of afferent fibers which have their origin in the lungs and heart. Impulses travel up the vagus nerves to the brain and activate vasodilator centers which cause peripheral vasodilatation through the sympathetic nerves. Jarisch and Richter[2] demonstrated the presence of this reflex in animals with the circulation of the heart and lungs isolated from that of the body. Veratrum also reduces blood pressure in animals with the vagus nerves cut,[3] yet Krayer, Moe and Mendez[4] have been unable to show direct action upon the blood ves-

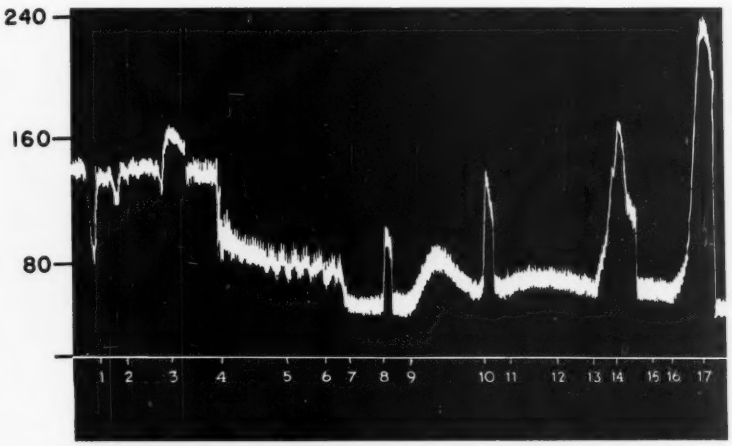

FIG. 3.—Effects of veratrum viride on cerebral chemoreceptors. (1) Intra-arterial injection of adrenaline 0.01 mg. (2) Intra-arterial injection of noradrenaline 0.01 mg. (3) Intra-arterial injection of histamine 0.1 mg. (4) Intra-arterial injection of veratrum 0.1 mg. (5) Intra-arterial injection of adrenaline 0.01 mg. (6) Intra-arterial injection of adrenaline 0.02 mg. (7) Intra-arterial injection of veratrum 0.1 mg. (8) Intravenous injection of adrenaline 0.01 mg. (9) Intravenous injection of renin 0.15 cc. (10) Intravenous injection of adrenaline 0.01 mg. (11) Intra-arterial injection of adrenaline 0.01 mg. (12) Intra-arterial injection of histamine 0.1 mg. (13, 14) Cerebral ischemia 60 seconds. (15) Intra-arterial injection of adrenaline 0.02 mg. (16, 17) Cerebral ischemia 120 seconds.

sels. This suggests a central action in addition to the vasodepressor effects of the von Bezold reflex. Our data support this view.

Veratrum injected into the body of the recipient animals with vagus nerves intact caused a fall in blood pressure (18 to 60 mm. Hg), but if the vagus nerves were cut or the animal decapitated, veratrum circulating in the body had no effect upon the blood pressure (table 3).

In five experiments veratrum was circulated through the recipient's head. A single injection caused a fall of blood pressure in both the donor and the recipient dogs' bodies. The pressure of the donor returned to control levels within 45 minutes while that of the recipient persisted at the lower levels for the two to four hours they were observed.

It is of particular interest that during this period the peripheral effects of the central action of all other drugs tested were abolished, yet acute cerebral ischemia induced by clamping the perfusing artery caused a sharp increase in the recipient dog's blood pressure (80 to 180 mm. Hg) (fig. 3).

Discussion

These data furnish further evidence for the presence of cerebral chemoreceptor buffers and aid in elucidation of the mechanism of action of veratrum viride.

It was previously shown[1] that adrenaline and noradrenaline were peripheral vasodilators when acting solely on the central nervous system with the carotid sinuses and aortic depressor nerves destroyed. This depressor effect was independent of change in the perfusion pressure within the head whether the change was induced by a pump, drugs acting upon the donor dog's pressure, or bleeding of the donor animal. Tournade[5] suggested that vasoconstriction and reduction of blood flow with hypoxia of the vasomotor centers might explain the mechanism of centrally induced peripheral vasodilatation. Schmidt and Pierson,[6] however, measured blood flow through the medullary area with a thermocouple and found it to be unaltered by adrenaline. This, among other reasons, made us conclude that there were previously unrecognized cerebral chemoreceptor buffers.

The behavior of the arterial pressure of the recipient animals in the experiments after injection of histamine and veratrum further separates these chemoreceptors from other nervous mechanisms known to influence peripheral blood pressure. Histamine injected intra-arterially into the perfusion circuit of the recipient animal's head usually caused sharp rise of peripheral blood pressure. In some animals repeated injections apparently exhausted this mechanism or tachyphylaxis supervened, because after one to two hours no further pressor responses could be elicited in the body. If cerebral ischemia were now induced by clamping the artery perfusing the isolated head, a sharp rise in blood pressure occurred, indicating that the receptors sensitive to reduced blood flow were still capable of inducing a rise in arterial pressure.

The peripheral pressor effects induced by cerebral ischemia and that dependent upon stimulation of the chemoreceptors were further delineated by centrally acting veratrum. Intra-arterial injection of this drug caused a prolonged fall of peripheral blood pressure and development of refractiveness to pressor and depressor drugs. Ischemia was still capable of causing a sharp pressor response. Thus, not only are there cerebral centers which cause peripheral vasodilatation when stimulated by vasoconstrictor drugs and peripheral vasoconstriction in response to centrally acting vasodilator drugs, but they can be inactivated without altering the areas stimulated by ischemia.

If veratrum is injected into the body of a recipient animal with intact vagus nerves, a fall in blood pressure results, although none of the drug reaches the central nervous system. If the vagus nerves were cut or the dog decapitated, veratrum had no effect upon the blood pressure in the body of the animal, which confirms the observation of Krayer, Moe and Mendez[4] that the blood vessels themselves are not responsive to veratrum.

Because blood pressure falls when veratrum is injected into dogs that had received atropine or in which the vagus nerves were cut, Krayer, Moe and Mendez assumed that the central nervous system was either stimulated or inhibited so that peripheral vasodilatation oc-

curred. Our experiments demonstrated the assumed central action. When the drug acted solely upon the nervous system of a dog there was a prompt and prolonged reduction of peripheral blood pressure. This centrally induced hypotension might occur because of inhibition of existing vasomotor tone of central origin or by direct stimulation of a vasodilator mechanism. Since we have shown that veratrum is inhibitory to one system, the chemoreceptors, it is likely that its hypotensive effects are likewise the result of inhibitory action. If this is true, the vasomotor tone apparently depends upon centers other than those responsible for the acute hypertension resulting from cerebral ischemia, since veratrum leaves the latter mechanism intact.

Summary

Substances which are pressor or depressor in intact animals were tested for their effects upon peripheral blood pressure when acting upon the cerebral chemoreceptors of dogs with carotid sinuses inactivated and vagus nerves sectioned. Tests were made by perfusing the drugs through the circulation of the brain which was completely isolated from the body. The pressor drugs, barium chloride and nicotine, caused hypotension and respiratory stimulation.

Histamine caused a pressor reaction in more than three-fourths of the experiments, the rise often being preceded by a slight fall. In the remaining experiments the response was depressor. In some experiments, due to exhaustion of the chemoreceptor mechanism or to tachyphylaxis, histamine ceased to cause a pressor reaction, yet ischemia caused a sharp rise in blood pressure. Mecholyl regularly produced a striking rise of the peripheral blood pressure.

Veratrum viride reduced blood pressure when injected into the isolated circulation of the body of the recipient dog if the vagi were intact. It had no effect if they were sectioned. When injected into the circulation of the brain, veratrum caused a marked fall of peripheral blood pressure which persisted for the duration of the experiment (two to four hours). Further, it blocked the chemoreceptors so that no other drugs injected into the circulation of the brain influenced peripheral blood pressure, although cerebral ischemia still caused a rise in peripheral pressure.

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The Cardiovascular Effect of Induced Controlled Anoxemia

A Preliminary Ballistocardiographic Study of Normal Subjects and a Few Patients with Suspected Coronary Artery Disease

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Cardiovascular responses were studied by means of the ballistocardiograph and electrocardiograph in 16 normal subjects and 11 patients with suspected coronary artery disease before, during and after the induction of oximetrically controlled anoxemia. Progressive and significant increases occurred in cardiac output, pulse rate, left ventricular work, maximum cardiac force and pulse pressure during anoxemia in all of the normal subjects and in the 5 patients whose ballistocardiograms allowed the calculation of these variables. The increase in cardiac output resulted almost entirely from an acceleration of cardiac raté. In the normal subjects control ballistocardiograms were normal in form and remained normal throughout anoxemia. Of the patients, 1 with normal, 2 with borderline and 1 with abnormal ballistocardiograms became abnormal or more abnormal. Two of the patients had a positive electrocardiographic test for coronary insufficiency while the test was negative in all of the normal subjects.

The linear relationship between left ventricular work and arterial oxygen saturation suggests that when cardiovascular function is tested by means of anoxemic stress the level of arterial desaturation should be controllable. This is made possible by the use of a variable oxygen-nitrogen mixture and an oximeter.

SINCE THE Pike's Peak expedition by Douglas, Haldane, Henderson and Schneider[1] in 1911, the physiologic effect of altitude and anoxemia has been the subject of considerable scientific interest; the studies conducted by these physiologists formed the basis for most of the investigative work which has followed. Interest in anoxemia has sprung not only from the frequency of its occurrence in clinical medicine and from its use as a test of cardiac function but also, during World War II, from its importance in the field of military aviation.

The results from many of the earlier studies of the circulatory changes consequent to anoxemia were conflicting and inconclusive. In their Pike's Peak expedition Douglas and his coworkers[1] attempted to estimate the change in cardiac output resulting from high altitude ("subacute" anoxemia) by the use of a prototype of the present day ballistocardiograph. Using this apparatus, which was the simplified version of a more elaborate instrument developed by Henderson in 1905,[2] the conclusion was reached that stroke volume and cardiac output were only slightly increased by the reduced oxygen tension at the peak of the 14,109 ft. mountain.

While some investigators[3–6] have held that anoxemia either reduces cardiac output or produces no change, Sands and DeGraff in 1925[7]

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This work was done while one of us (W.R.S.) was John D. Archbold Fellow in Medicine, and another (R.P.) was U. S. Public Health Service Post-Doctorate Fellow.

reported an increase in cardiac output which resulted from increases both in stroke volume and in pulse rate. Shortly thereafter Harrison and his co-workers,[8, 9] using the direct Fick method in unanesthetized dogs, reported consistent, uniform results indicating that cardiac output increases during anoxemia. Since then these findings have been corroborated by a number of investigators using different methods of producing anoxemia and of measuring cardiac output.[10–16] The discordant results recently reported by Motley and associates,[17] who found that cardiac output decreased in all of 5 normal subjects after breathing a 10 per cent oxygen mixture for 10 minutes, were apparently due to an error in technic and have since been disclaimed by these workers.[18]

The lack of a simple method permitting rapid, serial determination of cardiac output while a gas is being administered has greatly hampered studies of anoxemia-induced cardiac output changes. However, Starr's[19] development of the ballistocardiograph as a means of estimating relative changes in cardiac output has provided an instrument which is admirably suited to experiments of this kind.

Using a vertical ballistocardiograph, Starr and McMichael[15] studied the circulatory changes occurring in 21 normal persons subjected to simulated altitudes of 16,000 to 18,000 ft. in a low pressure chamber. It was found that the mean fall in arterial oxygen saturation of 21 per cent resulted in an average increase in cardiac output of 39 per cent. A similar increase in cardiac output has recently been reported by Steele and Galdston[14] using the ballistocardiograph and by Keys and co-workers[13] using an x-ray cardiac output technic.

Since Resnik[20] in 1925 suggested that anoxemia may produce a different effect on a damaged heart than on a normal one, interest in anoxemia as a means of testing cardiac function has gradually become more widespread. In 1939, Levy, Bruenn and Russell[21] reported their clinical test for coronary insufficiency which has since become a standard method. These investigators, using a gas mixture containing 10 per cent oxygen, evolved criteria for normality based on the statistical difference of electrocardiographic response between normal subjects and patients with coronary artery disease.[22, 23] Since their early papers a large number of reports have appeared in the literature relating to the diagnostic use of anoxemia in clinical coronary artery disease.[24] The principle upon which its use is based is that a heart in which the coronary circulation is relatively fixed and inflexible will manifest definite electrocardiographic disturbances at a degree of oxygen restriction which will produce little or no disturbance in a heart without impairment of coronary circulation.

While the effect of anoxemia on the electrical activity of the heart in subjects with coronary artery disease has been extensively explored, there has been little investigation of its effect on circulatory mechanics in such patients. It seems reasonable to believe that other physical functions, such as stroke volume, cardiac output, cardiac work and ejection velocity may also be altered in an abnormal fashion in patients with impaired coronary blood flow.

The purposes of this study were twofold: (1) to determine the type and magnitude of some of the circulatory changes occurring in young normal individuals subjected to acute progressive anoxemia, and (2) to study these changes in subjects with suspected or proved coronary artery disease.

Shortly after this study began it became apparent that suitable patients with coronary artery disease would be difficult to secure because the majority of such patients had ballistocardiograms which were abnormal in form at rest and therefore not suitable for the calculation of cardiac output or related variables.[25] As a result of this difficulty in finding proper candidates, the group which was finally accumulated was somewhat heterogeneous clinically; a few presented classical angina pectoris, others had chest pain which suggested coronary disease but was atypical, and finally, 2 did not have chest pain suggestive of coronary disease but were included for other reasons.

Apparatus and Method

The arterial oxygen saturation of the blood was determined by the use of a Millikan automatically-compensated oximeter and was controlled by varying the oxygen concentration in an oxygen-nitrogen gas mixture administered through a mouthpiece

from a Heidbrink anesthesia machine. This method, previously described,[26] permits the induction of anoxemia at any rate desired and allows the use of standard levels of arterial desaturation in all subjects. The oximeter was calibrated by the administration of 100 per cent oxygen at the beginning of each test and this procedure was repeated at the end of the test as an accuracy check.

Electrocardiograms were taken in most of the normal subjects and in all of the patients on room air (before and after the test), on 100 per cent oxygen and at various levels of arterial desaturation. In most cases the three standard limb leads and four precordial leads were taken. A Cambridge string galvanometer electrocardiograph machine was used. The use of four fixed precordial leads and a lead selector switch allowed multiple precordial records to be taken rapidly from exactly the same positions in each of the patients suspected of having coronary artery disease. In these subjects a complete electrocardiographic survey was made just prior to the beginning of the test; this included standard and unipolar limb leads and six unipolar precordial leads. In addition, throughout the period of anoxemia, electrocardiograms (usually V_4) were taken almost continuously with a Sanborn direct-writing instrument. Control (room-air) electrocardiograms were classified as "normal," "abnormal" or "borderline" in conformity with generally accepted standards. The Levy[23] criteria were adhered to in evaluating the results of the anoxemia tests. Where Master tests were carried out Master's[27] criteria for a positive exercise test were used.

The ballistocardiograph was of the Starr high-frequency, horizontal type. The natural frequency of this bed loaded with 150 pounds of dead weight was approximately 10.5 cycles per second. An electrocardiogram (lead II) was recorded as a time base for the ballistocardiogram. The instrument was calibrated so that 280 Gm. produced a 1 cm. deflection of the baseline.

All ballistocardiograms were classified as "normal," "abnormal" or "borderline" on the basis of ballistocardiographic form; no precise criteria for normality of form yet exist.

In calculating cardiac output the Starr area formula,[28] as modified by Tanner,[29] was used:

$$S.V. = 100\sqrt{2I + J\sqrt{c}}$$

Three pairs of complexes (each consisting of a large and a small) were used for each stroke volume calculation. Pulse rate was estimated by counting the number of beats in a 20 second interval (to nearest 0.1 beat) and multiplying by 3.

Maximum cardiac force (M.C.F.) values were calculated according to Starr's[30] formulas:

$$M.C.F./Beat = I + J + I_2 + J_2$$

where I_2 and J_2 are amplitudes of the I and J waves in a large complex and where I and J are amplitudes of the I and J waves in a small complex; and

$$M.C.F./Min. = M.C.F./Beat \times Pulse\ Rate$$

The mean of three sets of complexes was used for each calculation.

Blood pressure was determined by the auscultatory method repeatedly during the control period on room air and then at intervals throughout the remainder of the test. Left ventricular work was estimated by use of the formula

$$LV\ Work = 0.0135 \times C.O. \times Mean\ B.P.$$

where left ventricular work is expressed in Kg. meters per minute, cardiac output in liters per minute and where mean blood pressure represents the simple arithmetic mean of the systolic and diastolic blood pressures.

The subjects studied fell into two groups. The first, which we shall refer to hereafter as the "normal group," included 16 young persons between the ages of 19 and 32 (mean 26) who were adjudged healthy by all of the usual methods of clinical examination.* There were 12 men and 4 women in this group. Twelve of these were medical students who, as a part of a long range program being conducted by one of us (C.B.T.), had undergone an intensive cardiovascular survey including complete history and physical examination, electrocardiograms, chest x-rays, cold pressor tests, Master tests, as well as other physiologic and psychologic studies.

The second group, which shall be referred to as the "patient group," included 11 persons who for one reason or another were suspected of having coronary artery disease. Nine of the 11 subjects in this group had symptoms suggestive of angina pectoris, either typical or atypical. The remaining 2 had chest discomfort which did not suggest pain of coronary origin, but 1 had a positive Master test and the other an abnormal resting ballistocardiogram; they were therefore grouped with the other 9 cases for the determination of mean values for the several physiologic variables. None of them had enlarged hearts, abnormal control electrocardiograms or blood pressures over 150/100 (although 3 had had values above this level on previous occasions). There were 8 men and 3 women. Their ages ranged from 38 to 62 with a mean of 49. None of these subjects was ill at the time of the anoxemia test and all were ambulatory.

No test was done within one and one-half hours after a meal and in all cases a period of rest of 30 minutes or more in the supine position was allowed.

* In one of the medical students a diagnosis of infectious mononucleosis was made the day after his anoxemia test.

While the earpiece of the Millikan oximeter was warming up, a set of control observations (ballistocardiogram, electrocardiogram and blood pressure) was made and repeated 10 minutes later. The subject was allowed to breathe room air through the mouthpiece for a short time and was then switched to 100 per cent oxygen in order to set the oximeter scale. In some cases the subject was allowed to breathe 100 per cent oxygen for three minutes after which another set of observations was made; in others this three minute oxygen breathing period was given at the end of the test while in a few it was given before *and* after anoxemia.

The subject was switched back to room air for another set of observations and then to the oxygen-nitrogen mixture. The oxygen concentration was gradually reduced so that the induction of anoxemia was smooth and without large fluctuations in arterial saturation. The subject was leveled off at predetermined saturation levels, usually 85 per cent, 80 per cent, 75 per cent and 70 per cent, and a set of observations was made at each level. In a few cases the subject was maintained at the lowest level of saturation (usually 70 per cent) for periods of 10 to 15 minutes, and observations were made at the beginning and end of this period. Anoxemia was terminated by switching to 100 per cent oxygen (which the subject was allowed to breathe for three minutes) and another set of observations was made. A final set, obtained about 10 minutes after the subject had been switched back to room air, concluded the test.

In calculating the results of the test, the two initial room air observations for each variable were averaged to give a single control figure to which all other values were referred as "percentage change from control." In summarizing the results for a whole group, all individual observations at a given saturation level were averaged to give a "mean percentage change" figure for that saturation level. The means, the standard deviations, the standard errors of the means and the ranges are all expressed in percentages referred to the room air controls (0 per cent). Not all of the subjects were studied at all of the predetermined saturation levels; for example, in the normal group, 3 were studied at 85 per cent, 10 at 80 per cent, 15 at 75 per cent and 13 at 70 per cent. Furthermore, a few observations were made at saturations between 85 per cent, 80 per cent, 75 per cent and 70 per cent; where this occurred the observations were grouped with the closest of these four. In several subjects more than one set of observations were made at the same saturation level; these were averaged to give a single figure for that saturation level.

A difference between any mean value and the control is considered statistically significant when the difference between mean and control (0 per cent) is greater than twice the standard error of the difference.

Results

Normal Group

In order to define as clearly as possible the cardiovascular changes consequent to anoxemia, the following ten variables were studied in each of the 16 subjects at the several arterial oxygen saturation levels: (1) cardiac output, (2) pulse rate, (3) stroke volume, (4) left ventricular work, (5) maximum cardiac force per beat (M.C.F./beat), (6) maximum cardiac force per minute (M.C.F./min.), (7) mean blood pressure, (8) pulse pressure, (9) ballistocardiographic form, and (10) electrocardiographic changes.

Table 1 summarizes the results obtained in the 16 anoxemia tests and includes all of the variables except ballistocardiographic form and electrocardiographic changes. The variables are plotted as mean percentage deviations from the control values in the figures 1 and 2. The ballistocardiographic tracings from a normal subject are shown in figure 3.

Cardiac Output. As will be seen in figure 1, the changes in cardiac output resulted almost entirely from changes in pulse rate, since stroke volume changed but little during the test. The mean changes in cardiac output were consistent and progressive although this was not always the case in the individual subject, for in a few the percentage increase in cardiac output was not as great at 70 per cent as at 75 per cent saturation. No normal subject failed to increase his cardiac output during anoxemia. Figure 4*A* is a scatter diagram of the individual cardiac output observations at the various saturation levels. It is evident that there is considerable variability in response; this variability increases as the arterial saturation decreases and is small at room air (96 per cent) and 100 per cent saturation. In figure 4*B* are shown the grouped means at the several saturation levels along with the standard deviations and the standard errors of the means. It is clear that there is essentially a linear relationship between cardiac output and arterial oxygen saturation. The fall in arterial oxygen saturation from 96 per cent to 70 per cent (26 per cent) produced a mean increase in cardiac output of 42.7 per cent. In figure 4 the cardiac

TABLE 1.—*Summary of Cardiovascular Changes during Anoxemia Test in Sixteen Normal Subjects*

	Control Room Air 96%	100% O_2 Before Test	Room Air 96%	85%	80%	75%	70%	100% O_2 After Test	Room Air After Test 96%
Pulse Rate									
Means-Absolute	68.9	67.6	68.7	82.6	87.2	91.7	94.3	61.2	63.5
Mean % Change		*−1.9*	*−0.4*	*+19.9**	*+26.7**	*+33.0**	*+36.8**	*−11.2**	*−7.9**
Range		−7.7	−5.9	+16.0	+13.8	+14.2	+11.4	−32.0	−17.0
		+9.9	+9.4	+23.9	+47.3	+62.9	+59.0	+5.2	+1.5
S.D.		±5.9	±3.9	±3.2	±10.0	±13.4	±13.3	±9.6	±5.3
S.E. of Mean		±1.8	±1.3	±1.9	±3.2	±3.5	±3.7	±2.9	±1.3
No. of Subjects	16	11	9	3	10	15	13	11	16
Stroke Volume									
Means-Absolute	92.3	91.0	90.8	90.8	93.1	92.1	94.3	90.4	92.5
Mean % Change		*−1.4*	*−1.6**	*−1.6*	*+0.9*	*+0.2*	*+2.2*	*−2.1*	*+0.2*
Range		−8.3	−5.0	−3.0	−12.0	−15.6	−7.5	−16.3	−10.2
		+6.5	+1.8	−0.6	+7.8	+12.3	+16.2	+12.3	+11.4
S.D.		±4.2	±1.9	±2.1	±5.4	±6.1	±7.1	±7.3	±5.7
S.E. of Mean		±1.3	±0.6	±1.2	±1.7	±1.6	±2.0	±2.2	±1.4
No. of Subjects	16	11	9	3	10	15	13	11	16
Cardiac Index									
Means-Absolute	3.48	3.34	3.42	4.14	4.45	4.71	4.97	3.05	3.20
Mean % Change		*−3.9**	*−1.9*	*+18.8**	*+27.8**	*+35.3**	*+42.7**	*−12.3**	*−8.0**
Range		−13.2	−10.5	+12.7	+6.8	+14.2	+20.4	−38.2	−19.5
		+1.0	+7.4	+24.6	+58.1	+68.8	+84.9	+4.0	+1.5
S.D.		±3.8	±5.0	±4.9	±14.4	±17.0	±20.3	±10.8	±6.1
S.E. of Mean		±1.1	±1.7	±2.8	±4.6	±4.4	±5.6	±3.3	±1.5
No. of Subjects	16	11	9	3	10	15	13	11	16
L.V. Work									
Means-Absolute	8.12	8.19	8.09	10.43	10.97	11.32	11.26	7.56	7.77
Mean % Change		*+0.8*	*−0.4*	*+28.5**	*+35.1**	*+39.4**	*+51.0**	*−6.9*	*−4.3**
Range		−5.8	−15.5	+21.9	+23.7	−10.2	+28.5	−35.2	−18.7
		+4.6	+11.2	+35.0	+58.8	+73.8	+108.4	+21.1	+7.1
S.D.		±3.8	±7.3	±6.6	±10.9	±23.3	±25.2	±13.9	±7.9
S.E. of Mean		±1.3	±2.6	±4.7	±3.5	±6.2	±7.3	±4.2	±2.1
No. of Subjects	15	8	8	2	8	14	12	11	14
M.C.F./Beat									
Means-Absolute	33.1	32.3	31.8	36.5	36.7	38.7	43.2	30.2	31.4
Mean % Change		*−2.5*	*−3.8**	*+10.1*	*+11.0**	*+16.8**	*+30.7**	*−8.8**	*−5.0*
Range		−14.5	−12.5	−2.2	−16.2	−22.1	+11.8	−29.9	−24.6
		+17.6	−0.2	+19.0	+29.4	+59.2	+81.9	+17.9	+13.1
S.D.		±8.1	±3.5	±9.0	±12.9	±18.7	±21.1	±15.0	±12.2
S.E. of Mean		±2.4	±1.2	±5.2	±4.1	±4.8	±5.6	±4.5	±3.1
No. of Subjects	16	11	9	3	10	15	13	11	16
M.C.F./Minute									
Means-Absolute	2275	2180	2200	3010	3230	3710	4165	1850	1986
Mean % Change		*−4.2*	*−3.3*	*+32.5**	*+42.2**	*+63.3**	*+83.3**	*−18.7**	*−12.7**
Range		−19.7	−18.8	+15.0	+1.8	+9.0	+49.9	−53.8	−34.7
		+9.9	+9.1	+41.9	+81.6	+140.0	+189.4	+6.3	+6.3
S.D.		±8.5	±8.1	±12.4	±23.6	±35.0	±45.4	±17.0	±13.6
S.E. of Mean		±2.6	±2.7	±7.2	±7.5	±9.0	±12.6	±5.1	±3.4
No. of Subjects	16	11	9	3	10	15	13	11	16
Pulse Pressure									
Means-Absolute	44.6	44.1	44.2	46.2	49.6	57.3	61.2	43.3	41.7
Mean % Change		*−1.1*	*−0.8*	*+3.5*	*+11.2**	*+28.5**	*+37.2**	*−10.2**	*−6.5*
Range		−13.6	−9.8	−9.8	−5.9	−15.1	−10.0	−34.9	−30.0
		+7.7	+11.8	+16.9	+30.3	+194.0	+229.2	+7.9	+16.9
S.D.		±5.8	±7.0	—	±11.8	±49.7	±26.9	±15.6	±13.3
S.E. of Mean		±2.1	±2.5	—	±4.2	±13.3	±7.8	±4.9	±4.9
No. of Subjects	15	8	8	2	8	14	12	10	14

TABLE 1.—*Continued*

	Control Room Air 96%	100% O_2 Before Test	Room Air 96%	85%	80%	75%	70%	100% O_2 After Test	Room Air After Test 96%
Mean Blood Pressure									
Means-Absolute	99.4	103.7	100.8	108.9	101.8	100.0	103.9	105.8	102.9
Mean % Change		*+4.2**	*+1.5*	*+8.2*	*+2.2*	*+0.7*	*+4.5**	*+6.5**	*+3.6**
Range		−2.3	−5.8	—	−11.5	−23.0	−49.3	−4.9	−4.9
		+7.3	+6.0	—	+10.7	+8.2	+13.3	+16.4	+9.0
S.D.		±2.6	±4.1	—	±6.0	±8.1	±5.6	±5.1	±4.4
S.E. of Mean		±0.9	±2.2	—	±2.1	±2.2	±1.6	±1.5	±1.2
No. of Subjects	15	8	8	2	8	14	12	11	14

* Denotes that change is statistically significant.

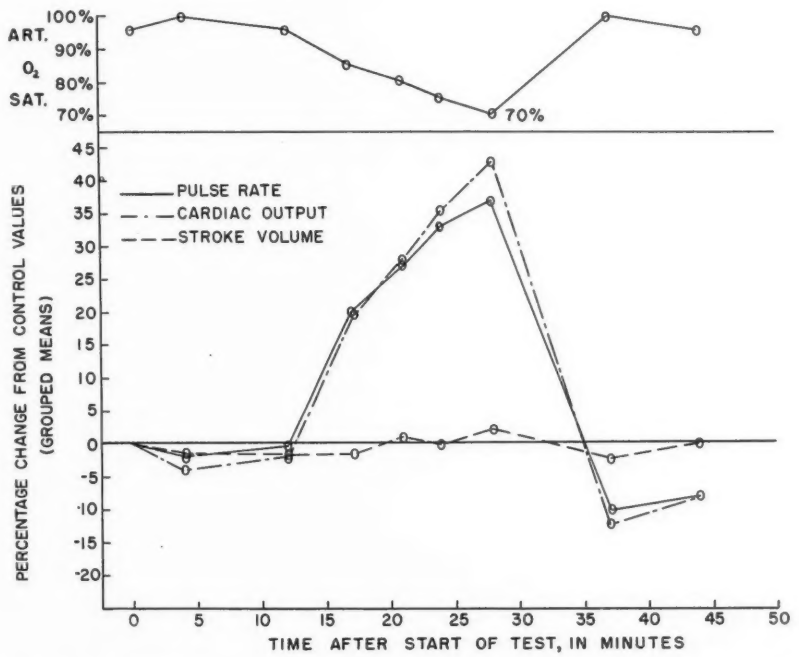

FIG. 1. The "average" ballistocardiographic anoxemia test. This graph demonstrates changes in cardiac output, stroke volume and pulse rate in 16 normal subjects during anoxemia and shows the relationship between these variables and arterial oxygen saturation (upper curve). Note that the increase in cardiac output is due almost entirely to the increase in pulse rate.

output values at 100 per cent saturation and room air, both after the test, are plotted with symbols which differ from the rest because these values were consistently lower than those at the same saturation levels before the induction of anoxemia. Since this appeared to be a result of the physical and/or psychic stress of the anoxemia test, these values were not included in the calculations of the correlation coefficient or regression equation. Three minutes of 100 per cent oxygen breathing before the test decreased the cardiac output 3.9 per cent, whereas the same procedure at the end of the test decreased it 12.3 per cent; this difference is statistically significant.

Although there were only 4 women in the group, their cardiac output changes were considerably greater than those in men. The mean

increase in cardiac output of the 3 women tested at 70 per cent was 73.8 per cent, whereas the average for the 10 men was 33.4 per cent; the mean increase in the 4 tested at 75 per cent was 49.2 per cent whereas the average for the men was 32.3 per cent.

As with cardiac output, there is a strong linear relationship between pulse rate and arterial oxygen saturation through the range employed. Figure 5 shows the mean pulse rate values along with their standard deviations and standard errors. The scatter of the individual pulse

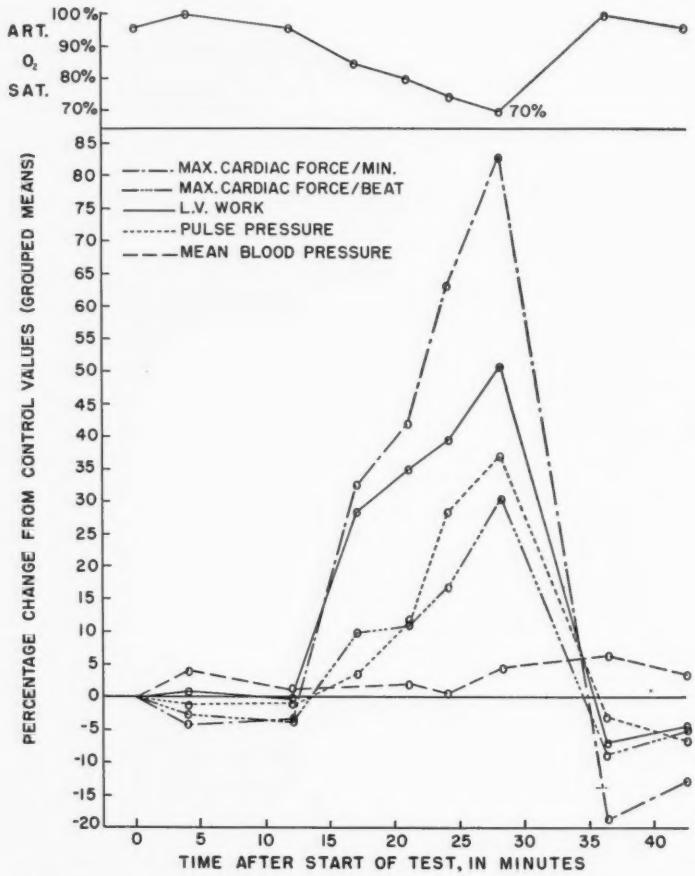

FIG. 2. The "average" ballistocardiographic anoxemia test. This graph demonstrates changes in left ventricular work, maximum cardiac force, pulse pressure and mean blood pressure in 16 normal subjects during anoxemia. All of these variables except mean blood pressure, bear a rough linear relationship to arterial oxygen saturation (upper curve).

Pulse Rate. The changes in pulse rate during anoxemia were similar to those in cardiac output since the latter was almost entirely dependent on the former (fig. 1). The average increase in pulse rate at 70 per cent saturation was 36.8 per cent (25.4 beats) and at 75 per cent saturation was 33.0 per cent (22.8 beats). rate values about their means is less marked than that in the cardiac output values. The difference in pulse rate on 100 per cent oxygen before the test and 100 per cent oxygen after the test is statistically significant.

Stroke Volume. Changes in stroke volume during anoxemia were small, variable and in-

significant (fig. 1). The largest mean stroke volume deviation was an increase of 2.2 per cent at 70 per cent saturation; however, individual values varied from −7.5 per cent to +16.2 per cent (S.D. = ±7.1 per cent).

Maximum Cardiac Force. These values, which actually represent mean I-J amplitude per beat and per minute, showed definite increases with anoxemia (fig. 2). The mean increase in maximum cardiac force per beat at 70 per cent saturation was 30.7 per cent; the scatter about this mean was considerable, as is evidenced by the standard deviation of ±21.1 per cent. None of the 13 subjects tested at 70 per cent failed to show an increase in I-J amplitude (maximum cardiac force per beat) but at 75 per cent saturation 2 of the 15 subjects showed values below their controls, −3.8 per cent and −22.1 per cent. The latter figure was from the only normal subject in whom the ballistic form was altered during anoxemia; in this case there was a progressive decrease in the depth of the I wave during the test.

The small number of observations and of their means makes it difficult to determine whether or not the relationship between maximum cardiac force per beat and arterial oxygen saturation is a linear one. However, the average deviation of the mean values from the line of best fit (relating maximum cardiac force and arterial oxygen saturation) is so small that there is no evidence that it is not linear within the range of saturation studied (70 per cent to 100 per cent).

There was a like progressive increase in

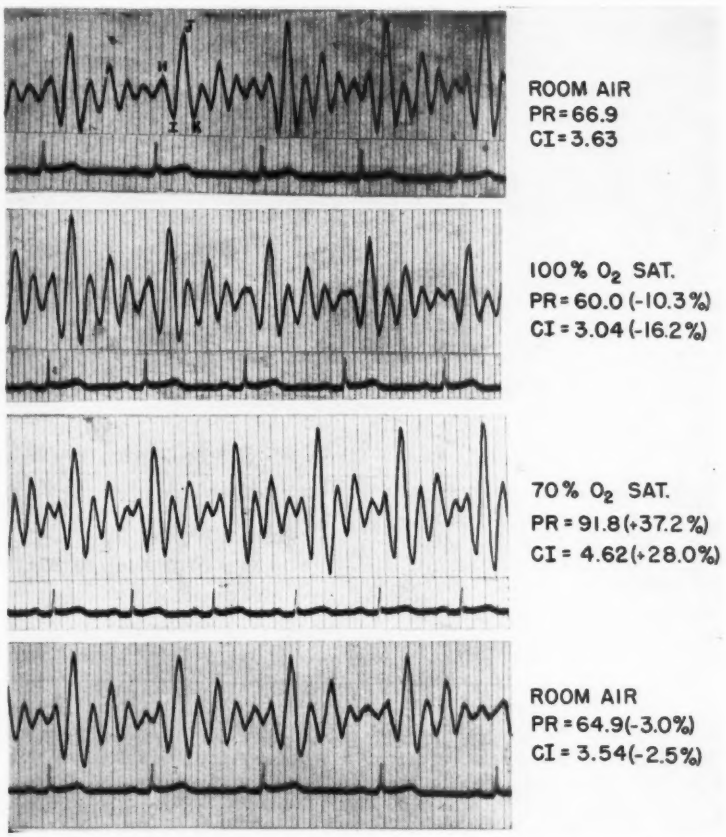

FIG. 3. Ballistocardiographic anoxemia test. Normal subject (J. W.).

maximum cardiac force per minute as the arterial oxygen saturation was decreased (fig. 2). The mean increase in maximum cardiac force per minute at 70 per cent was 83.3 per cent, and there was less scatter of individual observations than was the case with maximum cardiac force per beat.

The mean values of these calculations, in common with pulse rate and cardiac output, with changes in arterial oxygen saturation, and the "mean percentage change curve" (fig. 2) is roughly similar to those for the cardiac output, pulse rate and maximum cardiac force. Pulse pressure progressively increased as arterial oxygen saturation decreased; at 70 per cent saturation there was a mean increase in pulse pressure of 37.2 per cent. However, there was a large degree of scatter of the individual ob-

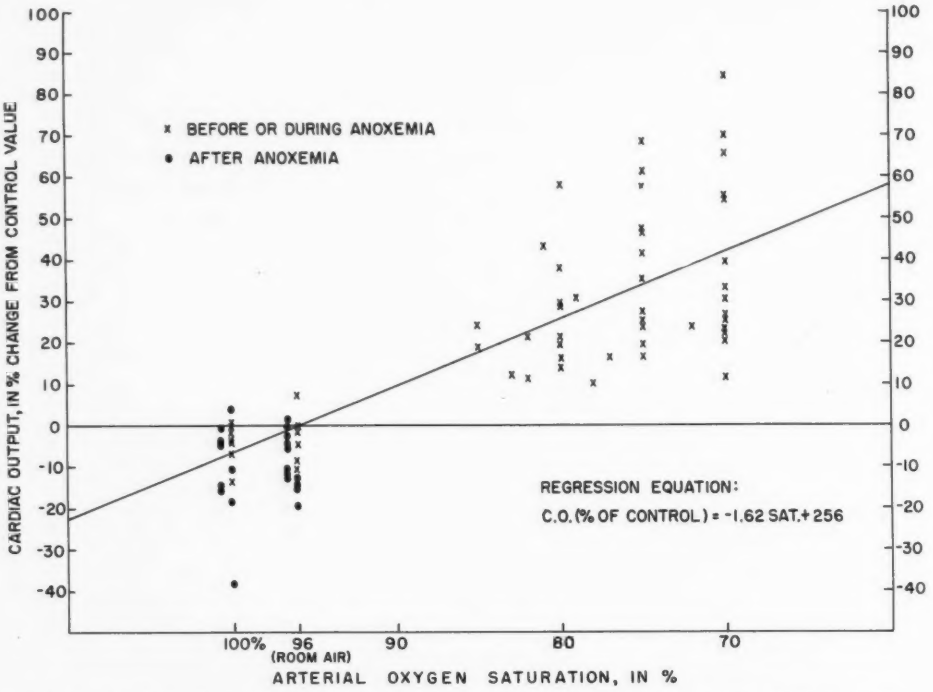

FIG. 4A. Percentage change in cardiac output during anoxemia. This scatter diagram demonstrates the relationship between arterial oxygen saturation and cardiac output. Note the individual variation in cardiac output at 70 per cent arterial saturation.

were decreased on 100 per cent oxygen and room air (after 100 per cent oxygen) before anoxemia and were further decreased at these two saturation levels at the end of the test.

Blood Pressure. The changes in mean blood pressure during anoxemia were generally small and insignificant, although a slight elevation at 70 per cent was significant. On 100 per cent oxygen before and after the test, mean blood pressure was slightly but significantly elevated.

Pulse pressure changes appear to correlate servations about the several means, as indicated by the ranges given in table 1.

It appears from these data that there is no definite correlation between pulse pressure and stroke volume.

Left Ventricular Work. Left ventricular work increased progressively as arterial oxygen saturation decreased. The "mean percentage change curve" (fig. 2) for left ventricular work is similar to that for cardiac output, to which it is related. The mean increase in left ventricular

work at 70 per cent saturation was 51.0 per cent. Scatter of the individual observations is somewhat greater than for cardiac output, but the average deviation of the several means from the line of best fit is small.

Ballistocardiographic Form Changes. Ballistocardiographic form was normal in the control tracings in all subjects. In no case did ballistic form become abnormal during anoxemia. In one case there was a progressive decrease in the depth of the I wave which produced a decrease in both the I-J amplitude and stroke volume; this alteration disappeared after the termination of anoxemia. A similar but more pronounced alteration in form occurred in this same subject immediately following a double Master exercise test. Figure 3 is illustrative of the consistency of ballistocardiographic form in the normal subject during anoxemia.

Electrocardiographic Changes. In all cases electrocardiographic changes were "physiologic" and similar in character and degree to those previously reported[31] on a larger group of normal subjects. In no case was there a positive test for coronary insufficiency. There were no arrhythmias or other electrocardiographic abnormalities.

Symptoms. There were no serious consequences of the anoxemia test and but few minor symptoms. In some cases slight dizziness was noted at the lower saturation levels. A small number of subjects developed hyperventilation during the test and it was noted that when this symptom appeared it usually did so at a relatively high arterial saturation level. In no case was hyperventilation so marked that the ballistocardiogram was rendered unsuitable for the calculation of cardiac output. There was no instance of chest pain or of syncope.

The majority of the tests were smooth and

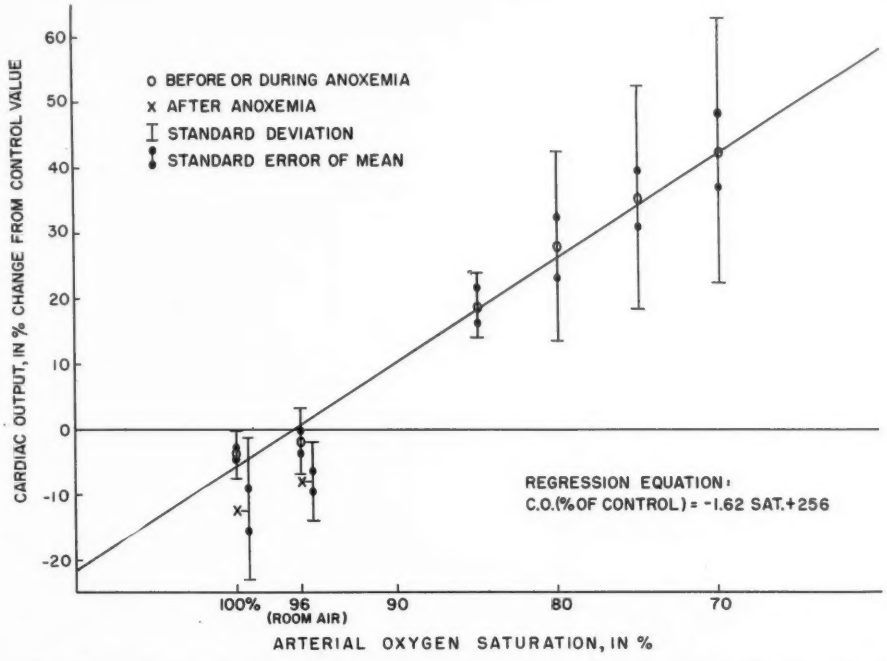

FIG. 4B. Percentage change in cardiac output during anoxemia (grouped means). This graph shows the mean cardiac output values (in per cent) at the several saturation levels along with their standard errors and the standard deviations. It will be noted that the relationship between arterial oxygen saturation and cardiac output is essentially linear.

the oximeter readings quite stable. Most of the subjects at the conclusion of the test stated that they were never aware of being anoxemic; this could probably be attributed to the gradual, smooth induction made possible by the variable oxygen concentration method employed in this study.

Patient Group

Table 2 is a summary of the changes in cardiovascular function in these 11 patients and is to be compared with table 1 of the normal group.* In only 5 subjects was it possible to calculate cardiac output. In 5 patients alterations of ballistic form in the control tracings did not allow this calculation to be made. In another (J. R.) ballistocardiographic form was normal in the control record but became so abnormal at 80 per cent saturation that cardiac output could not be calculated; this patient was therefore not included in those calculations where cardiac output was a factor.

When the "mean percentage change" values of this group of patients are compared with those of the normal group it will be seen that there is close similarity both in direction and in magnitude of change. However, the patients yielded somewhat lower values in most of the variables. The differences between these two groups are generally not statistically significant.

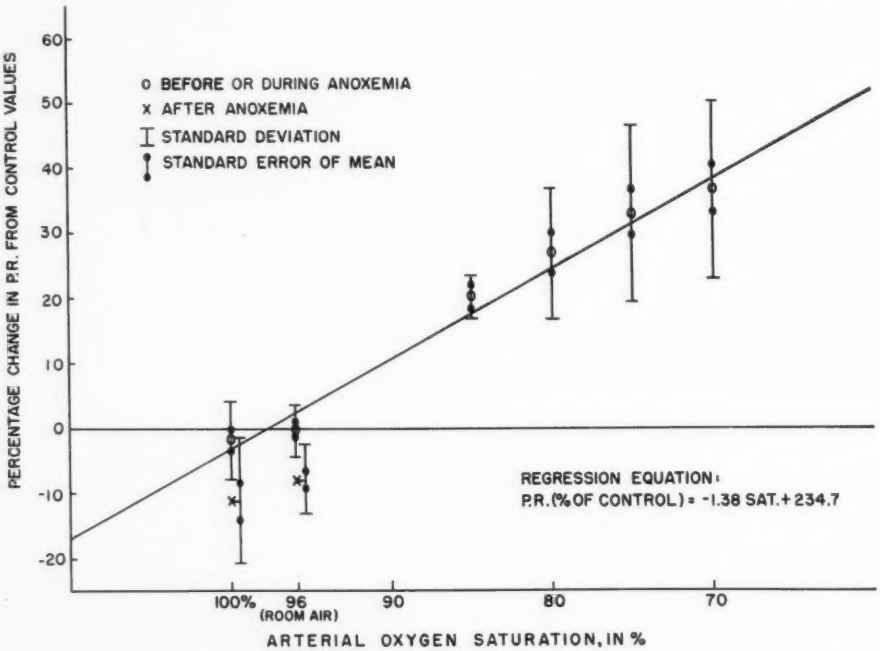

FIG. 5. Percentage change in pulse rate during anoxemia (grouped means). This graph shows that the relationship between pulse rate and arterial oxygen saturation is essentially linear. Note that the standard deviations about the means are smaller than those for cardiac output.

Table 3 shows the changes occurring in the electrocardiogram and the ballistocardiogram during the anoxemia test and includes the results of the Master test where it was carried out. It will be noted that the resting control ballistocardiogram was normal in 4 subjects, abnormal in 4 and borderline in 3. In one of the subjects (J. R.) with normal ballistocardio-

* It will be noted in table 2 that there are no columns for 100 per cent oxygen before test, room air (after 100 per cent oxygen) before test and 85 per cent saturation; the number of observations at these levels was too small to justify their inclusion.

TABLE 2.—*Summary of Cardiovascular Changes during Anoxemia Test in Eleven Patients with Suspected Coronary Artery Disease*

	Control Room Air 96%	80% Sat.	75% Sat.	70% Sat.	100% O_2 After Test	Room Air After Test 96%
Pulse Rate						
Means-Absolute	76.0	88.5	97.9	97.6	69.2	73.7
Mean % Change		*+16.4**	*+28.8**	*+28.4**	*−9.1**	*−3.1*
Range		+7.0	+17.1	+17.8	−20.4	−18.9
		+33.3	+43.3	+45.7	−1.4	+9.9
S.D.		±7.9	±9.3	±9.3	±5.7	±7.2
S.E. of Mean		±2.6	±3.1	±4.2	±1.8	±2.2
No. of Subjects	11	9	9	5	10	11
Stroke Volume						
Means-Absolute	79.9	84.2	77.6	87.1	76.5	79.1
Mean % Change		*+5.4*	*−2.9*	*+9.0**	*−4.2*	*−1.0*
Range		−1.7	−13.9	+6.0	−14.4	−6.1
		+15.3	+6.9	+11.4	+11.3	+13.4
S.D.		±7.2	±7.8	±2.2	±9.5	±7.3
S.E. of Mean		±4.2	±3.4	±1.3	±4.8	±3.3
No. of Subjects	5	3	5	3	4	5
Cardiac Index						
Means-Absolute	2.89	3.55	3.62	3.89	2.49	2.77
Mean % Change		*+23.0**	*+25.1**	*+34.6**	*−13.8**	*−4.2*
Range		+13.1	+21.1	+29.2	−25.4	−14.1
		+31.1	+30.1	+41.8	−2.0	+7.8
S.D.		±7.5	±3.9	±5.3	±8.6	±8.3
S.E. of Mean		±4.3	±1.7	±3.1	±4.3	±3.7
No. of Subjects	5	3	5	3	4	5
Left Ventricular Work						
Means-Absolute	7.65	9.75	10.02	10.62	6.53	7.15
Mean % Change		*+27.8**	*+31.0**	*+38.8**	*−14.6**	*−6.6**
Range		+12.9	+23.6	+29.9	−24.7	−13.8
		+31.3	+42.8	+51.2	−3.6	+3.4
S.D.		±11.0	±7.1	±9.1	±8.8	±6.2
S.E. of Mean		±6.4	±3.6	±5.3	±5.1	±3.1
No. of Subjects	4	3	4	3	3	4
Maximum Cardiac Force/Beat						
Means-Absolute	21.3	25.3	25.1	30.0	19.3	20.4
Mean % Change		*+18.7**	*+17.8**	*+41.1**	*−9.3**	*−4.1*
Range		+0.5	−8.0	+15.5	−27.2	−16.2
		+44.4	+37.5	+78.0	+14.4	+17.6
S.D.		±14.4	±13.7	±21.6	±12.1	±10.5
S.E. of Mean		±4.8	±4.6	±9.6	±3.8	±3.2
No. of Subjects	11	9	9	5	10	1
Maximum Cardiac Force/Min.						
Means-Absolute	1581	2174	2393	2893	1293	1415
Mean % Change		*+37.5**	*+51.4**	*+83.0**	*−18.2**	*−10.5**
Range		+15.1	+29.4	+44.5	−28.2	−24.3
		+72.5	+86.2	+160.0	−4.2	+11.3
S.D.		±17.8	±17.3	±41.6	±7.4	±11.4
S.E. of Mean		±5.9	±5.8	±8.3	±2.4	±3.4
No. of Subjects	11	9	9	5	10	11
Pulse Pressure						
Means-Absolute	49.8	54.3	58.5	63.7	50.4	47.3
Mean % Change		*+9.1**	*+17.4**	*+29.7*	*+1.2*	*−5.0*
Range		−2.0	−11.5	+1.8	−26.4	−29.4
		+24.0	+38.2	+56.9	+22.4	+11.8
S.D.		±8.9	±18.2	±17.7	±13.8	±11.3
S.E. of Mean		±3.0	±6.1	±7.9	±4.4	±3.4
No. of Subjects	11	9	9	5	10	11

TABLE 2.—*Continued*

	Control Room Air 96%	80% Sat.	75% Sat.	70% Sat.	100% O_2 After Test	Room Air After Test 96%
Mean Blood Pressure						
Means-Absolute	109.8	113.0	114.9	114.0	113.4	109.4
Mean % Change		+2.9*	+4.6*	+3.8	+3.3*	−0.4
Range		−4.0	−1.9	−1.9	−5.0	−8.7
		+9.3	+15.1	+11.5	+14.0	+4.8
S.D.		±4.0	±5.5	±4.8	±5.2	±4.7
S.E. of Mean		±1.3	±1.9	±2.1	±1.6	±1.4
No. of Subjects	11	9	8	5	10	11

* Denotes that change is statistically significant.

TABLE 3.—*Effect of Anoxemic Stress on the Electrocardiogram and on Ballistocardiographic Form**

Patient	History Suggestive of Angina Pectoris	Anoxemia Test					Master Test
		Induced Pain	BCG FORM		ECG		
			Control	Changes	Control	Result	
1. G. B.	Yes	Yes	Abn	More Abn	N	Pos.	Neg.
2. S. F.	Yes	Yes	B	Abn	B	Pos.	Neg.
3. H. H.	Yes	No	B	None	B	Neg.	—
4. E. L.	Yes	Yes	B	Abn	N	Neg.	—
5. L. M.	Yes	No	N	None	N	Neg.	—
6. M. R.	Yes	No	Abn	None	N	Neg.	—
7. D. R.	Yes	No	N	None	N	Neg.	Pos.
8. J. R.	Yes	No	N	Abn	B	Neg.	Neg.
9. J. S.	Yes	No	Abn	Improved	B	Neg.	—
10. M. DiG.	No	No	N	None	N	Neg.	Pos.
11. L. M.	No	No	Abn	None	N	Neg.	—

* N = Normal, B = Borderline, Abn = Abnormal, Pos = Postive and Neg = Negative.

graphic form at rest, the ballistocardiogram became definitely abnormal during anoxemia (fig. 6). In 3 other patients, borderline or abnormal control records became more abnormal. In one instance (J. S.) in which the control ballistocardiogram was abnormal, there appeared to be improvement in ballistic form during anoxemia, although it remained abnormal.

In 2 of the 4 patients in whom ballistocardiographic form became abnormal, or more abnormal, (G. B. and S. F.), there were electrocardiographic changes during anoxemia which satisfied Levy's criteria for a positive test for coronary insufficiency and in both chest pain was produced. In one (G. B.), shown in figure 7, the electrocardiographic changes occurred at 75 per cent saturation while in the other (S. F.) they occurred at 80 per cent saturation. It is of interest that previous Master tests on these patients had been negative. In fact, the disagreement between the anoxemia test (electrocardiographic) and the Master test in this small group was striking, for in 4 of the 5 cases where both tests were carried out there were discordant results. In each case where disagreement existed the ballistocardiographic findings tended to support the results of the anoxemia test and oppose those of the Master test.

Since there appeared to be no significant difference in the mean physiologic responses to anoxemia between this group and the control group of young adults, common physiologic patterns which differed from the group as a whole were sought among the following patients: (1) those with electrocardiographically positive anoxemia tests; (2) those who developed chest pain during the test; and (3) those in whom the ballistocardiographic form became

abnormal. However, no differences were found which were characteristic of any of these three categories. Indeed, no single physiologic response characteristic could be found which was common to the subjects forming any of these three categories. The only point of difference to be found was in the percentage deviation of the calculated maximum cardiac force values from the predicted values in the *control* ballistocardiogram. Maximum cardiac force per beat, referred to the predicted, averaged −49.5 per cent in the cases forming the three categories above while this average in the remaining cases was only −21.2 per cent; the maximum cardiac force per minute values deviated from the predicted by −58.7 per cent and −27.6 per cent, respectively.

The average duration of anoxemia in this group was 22 minutes and the average lowest arterial oxygen saturation value was 72.4 per cent.

There were no serious consequences of the test in these patients. Three of the subjects developed chest pain and in each case the test was terminated abruptly by the administration of oxygen. In one of these at 75 per cent saturation, pain was preceded by hyperventilation, dizziness, pallor and a fall in blood pressure from a control of 148/96 to 116/70; oxygen promptly relieved all symptoms. In no case were there convulsions, syncope, arrhythmias or ectopic beats. No difficulty was encountered in inducing or maintaining the desired degree of anoxemia in any of the patients.

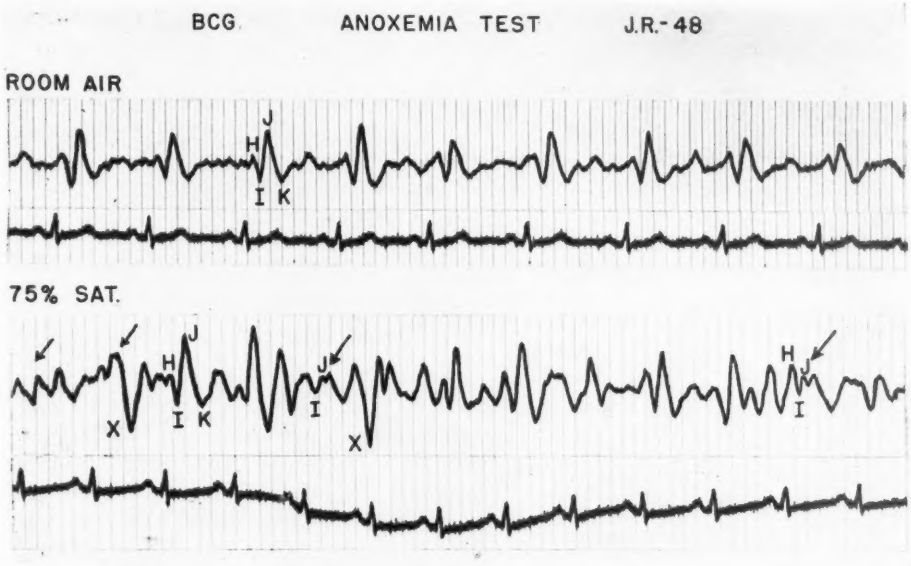

FIG. 6. Ballistocardiographic anoxemia test—patient with angina pectoris (J. R.). The ballistocardiogram, normal on room air, becomes abnormal at 75 per cent arterial oxygen saturation. Note the abnormal complexes (arrows), two of which show doubled J waves. At 75 per cent saturation the T wave of the electrocardiogram (lead II) has become isoelectric. The large deflections marked by crosses are diaphragmatic impacts.

DISCUSSION

There appears to be little doubt that cardiac output increases in the normal individual under conditions of acute anoxemia. The cardiovascular pattern of response to anoxemia is of interest. Our results suggest that there is a progressive increase in cardiac output as the arterial oxygen saturation decreases and that the increase in cardiac output is effected almost entirely by an acceleration of cardiac rate rather than by an increase in stroke volume.

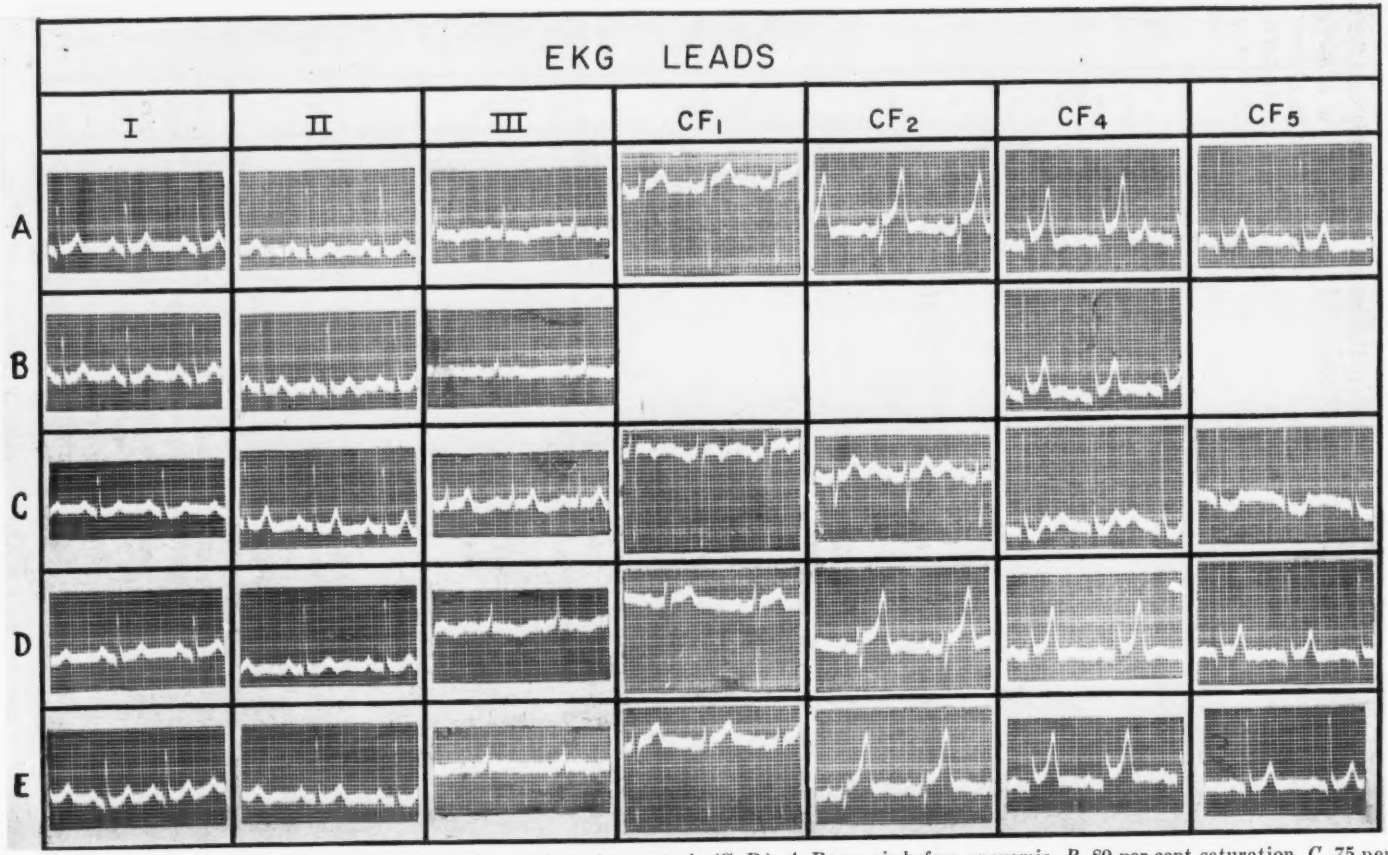

FIG. 7. Electrocardiographic anoxemia test—patient with angina pectoris (G. B.). *A*. Room air before anoxemia. *B*. 80 per cent saturation. *C*. 75 per cent saturation. *D*. 100 per cent saturation. *E*. Room air after anoxemia. Electrocardiograms taken before, during and after anoxemia illustrate a "positive" response. At 80 per cent saturation, total ST-T deviation (in the three standard leads and CF_4) was only 1.5 mm., a negative response, while at 75 per cent the total deviation was 5 mm., constituting a positive test for coronary insufficiency.

Similar conclusions have been drawn by Steele and Galdston[14]* (cardiac output = +32.3 per cent, PR = +33.1 per cent, and stroke volume = −1.3 per cent) who, like us, used a horizontal ballistocardiograph but who, unlike us, used either a gas mixture of constant oxygen content (10 per cent) or a low pressure chamber.

However, the earlier work by Harrison and co-workers,[8, 9] using the direct Fick method in dogs, indicated that under the conditions of their experiment the increases in cardiac output were due in the main to stroke volume increases. More recently Herbst and Manigold,[16] who used a pulse wave method for estimating cardiac output in normal human subjects, found that a 41.4 per cent increase in cardiac output was accompanied by a 11.3 per cent increase in stroke volume.

In the ballistocardiographic study by Starr and McMichael[15] there was a mean increase in cardiac output of 39 per cent, a figure similar to ours. However, this increase in cardiac output resulted from a 23 per cent increase in pulse rate and a 14 per cent increase in stroke volume. Starr has suggested that the difference in results (that is, in stroke volume contribution) may be accounted for by the difference in position of the subjects being tested, inasmuch as he used a vertical ballistocardiograph in which the subject sat upright.[32] The work of Keys and associates[13] is pertinent in this connection. Cardiac output was determined in 27 normal subjects by the roentgenkymographic method before and during anoxemia induced by the administration of a 10 per cent oxygen gas mixture; the subjects were all in the sitting position throughout the test. In spite of the erect position, cardiac output rose 37 per cent while stroke volume was unchanged, results similar to ours and those of Steele and Galdston.

It is possible that the effect of acute anoxemia on stroke volume is a matter of the degree of anoxemia, although in the human studies referred to above the levels of arterial desaturation utilized were roughly the same.

Earlier work by Sands and DeGraff[7] summarized in a recent review by Wiggers[33] suggested that mild or moderate anoxemia (above 75 per cent saturation) causes an increase in cardiac output without any increase in stroke volume whereas a greater degree of anoxemia produces an increase in both pulse rate and stroke volume; it should be noted, however, that cardiac output was not measured directly in this study but was inferred from changes in intracardiac, arterial and venous pressure in dogs. The range of arterial saturations employed in our study was not large enough to allow us to draw any conclusions in this regard.

It is worthy of note that most of the investigators who have studied anoxemia have found increases in pulse pressure during the test. In our normal group, pulse pressure increased an average of 37.2 per cent at 70 per cent saturation in spite of the absence of a significant increase in stroke volume. This appears to be a considerably greater increase than most other workers have noted.

We do not regard as inconsistent the finding that during anoxemia stroke volume is unchanged in spite of an increase in the I-J amplitude of the ballistocardiogram (as expressed by maximum cardiac force per beat). I-J amplitude is dependent on both systolic discharge (mass) and velocity of ejection. That the velocity of ejection is increased in anoxemia is suggested by the gradient of the ventricular pressure rise and the abbreviation of the isometric contraction phase.[7] Indeed, if stroke volume is to be maintained or increased in the presence of an increasing pulse rate, it must be through the medium of an increase in ejection velocity, a response demanded by the shortening of the ejection phase. It is for this reason that in Starr's stroke volume formula the $\sqrt{c}$ factor serves to neutralize the increase in ejection velocity (and in I-J amplitude) which results from the abbreviation of systole accompanying increased pulse rates. Thus, in our normal group at 70 per cent saturation, mean I-J amplitude increased 30.7 per cent but stroke volume increased only 2.2 per cent.

The changes in the electrocardiogram, pulse rate, blood pressure and pulse pressure noted in this study are similar to those in a group previously reported by Penneys and Thomas[31]

* The authors wish to thank Drs. Steele and Galdston for allowing us free use of their anoxemia data.

and to those of another group not yet reported.[34]

Our use of anoxemia as an agent for cardiovascular stress in the group of 11 subjects suspected of coronary artery disease was designed to uncover differences in the cardiovascular response patterns between patients of this type and normal subjects. It was reasoned that the patients with coronary artery disease might differ from the "normal" in several respects, including cardiac output response and ballistocardiographic form. Wiggers,[33] in commenting on the finding by Hilton and Eichholtz[35] and by Green and Wegria[36] that anoxemia causes a marked increase in coronary blood flow, stated that ". . . it is probable that myocardial stimulation (anoxemia) is converted into myocardial depression as soon as the augmentation of coronary blood flow cannot keep pace with the decreasing volumes of oxygen carried by the blood." In this study it was intended to select subjects with clearcut histories of coronary artery disease who had normal ballistocardiograms at rest in order to study changes in cardiac output and ballistocardiographic form during the stress of anoxemia. However, it soon became obvious that this would be difficult because of the high proportion of such patients who have abnormal ballistocardiographic form at rest, precluding cardiac output calculation. Unpublished data[25] indicate that the resting ballistocardiogram is abnormal in 80 per cent and abnormal or borderline in 90 per cent of such patients. Furthermore, since we excluded patients with abnormal electrocardiograms from the anoxemia test it became more difficult to find suitable subjects. Of a series of patients with coronary artery disease studied in this laboratory, 85 per cent have had an abnormal ballistocardiogram and/or electrocardiogram.[25] Four patients with abnormal ballistocardiograms were admitted to the study in order to determine whether ballistocardiographic form changes occur during anoxemia in subjects with this type of record.

The small number of cases in the "patient group" makes the drawing of conclusions difficult. However, in the 5 subjects in whom cardiac output could be calculated, there did not appear to be any significant difference from the normal group, nor did there appear to be any significant differences between the two groups in the other physiologic variables.

Makinson[37] studied two such groups with the ballistocardiograph using standardized exercise as the stress agent and obtained results in concord with ours. In nine patients with angina pectoris the mean increase in cardiac output immediately after exercise (48.8 per cent above the control) was almost identical to that in a group of normal subjects (47.4 per cent); both were similar to our findings at 70 per cent saturation. Mathers and Levy[38] have recently compared the anoxemia-induced changes in pulse rate and blood pressure in normal subjects with those in patients with coronary sclerosis; the average percentage deviations from the control values in the two groups were similar.

These data, while obviously not sufficient, suggest that the over-all cardiovascular response to stress by patients with angina pectoris may be normal in spite of the handicap imposed upon the heart by the restriction of coronary blood flow. Since Blumgart and his co-workers[39] have shown that in most patients with angina pectoris due to coronary arteriosclerosis there is complete occlusion of one or two of the three major coronary vessels, these findings testify to the efficiency of collateral circulation. The heart seems to retain its primary function, that of pumping blood, even when stress-induced ischemia may produce pain and electrical disturbances. The ability of the heart to increase its output when demands are placed on it does not indicate that it accomplishes this function in a normal fashion. Starr's studies in clinical coronary disease,[28, 40, 41] supported by his cadaver experiments,[30] suggest that one of the earliest alterations in circulatory dynamics in patients with coronary sclerosis is a change in the manner with which the heart ejects its blood. A normal heart contracts with a "snap," imparting to the blood a high ejection velocity early in systole, whereas a diseased heart is unable to do so, even though the *mean* ejection velocity and stroke volume in the two are the same. The normal heart produces a normal ballistocardiogram while the abnormal heart produces a ballistocardiogram in which the

form of the complexes is distinctly abnormal, reflecting the alteration in ejection velocity. Thus, even when cardiac output and other circulatory functions appear to be normal both at rest *and* under stress, an alteration in cardiac ejection is manifested by an abnormal ballistocardiogram *at rest* in the majority of patients with coronary disease.[25] In the patients who have normal ballistocardiograms at rest, one assumes that the restriction in coronary blood flow has not progressed far enough to interfere with systolic "snap"; if these patients are subjected to stress it seems likely that ejection velocity would not be able to keep pace with demands, and as a result the ballistocardiographic form would deteriorate. Our results and those of Makinson,[37] who found form changes following exercise, tend to support this hypothesis generally.

The ballistocardiographic form changes during anoxemia in this small group were not marked but were definite. On theoretic grounds one might expect that the development of form abnormality produced by this type of stress would be accompanied by a relative decrease in I-J amplitude (or maximum cardiac force per beat), reflecting a reduction in ejection velocity. In the single instance where a normal resting ballistocardiogram was converted to an abnormal one (fig. 6) the increases in both maximum cardiac force per beat and maximum cardiac force per minute were well above the means of the whole group; the small abnormal expiratory complexes were compensated for by the large inspiratory complexes. However, in the 2 cases where borderline ballistocardiograms were converted to abnormal ones, the changes in maximum cardiac force per beat were far below the general average. One of these (S. F.) showed a 36.5 per cent increase in maximum cardiac force per beat at 81 per cent saturation, but at 79 per cent ballistic form became abnormal and maximum cardiac force per beat dropped to only 2.7 per cent above the control. The other patient (E. L.) at 75 per cent saturation had increased her I-J amplitude by only 5.3 per cent; this observation was made during a mild hypotensive reaction characterized by pallor and a drop in blood pressure from 146/96 to 116/70. In both of these subjects chest pain was reproduced during anoxemia.

No definite conclusions regarding the effect of anoxemia on the ballistocardiographic form in subjects with coronary artery disease can be based on a group so small and heterogeneous. There is a possibility that early asymptomatic coronary artery disease can be detected by the deterioration of ballistocardiographic form during anoxemia when the ballistocardiogram at rest is normal. Makinson[37] has reported 2 subjects without detectable cardiovascular disease whose ballistocardiograms, normal at rest, became abnormal after exercise. Such stress technics may also prove of value in the study of those subjects in whom the history is suggestive of coronary disease but the results of other tests (ballistocardiograms, electrocardiograms, etc.) are equivocal. The continuing study of this technic may shed further light on this problem.

The use of the ballistocardiograph to determine cardiac output in accurate, absolute terms may be open to question but its use to determine relative changes in cardiac output on the same individual in acute experiments is much more secure. However, it should be pointed out that the constant (100) in the ballistocardiographic formula in current use was selected to give the best fit with cardiac output figures derived through cardiac catheterization under *resting* conditions.[29] While the two methods may agree closely under resting conditions it does not follow that this agreement will necessarily pertain under stress conditions. No such comparative study, carried out in a systematic manner, has yet been reported, but random observations suggest at least a fair degree of correlation between the two methods under conditions where there are large changes in cardiac output.

Where the ballistocardiograph is to be used to follow cardiac output and other physical functions of the heart and circulation under conditions of stress, we feel that the induction of anoxemia is the method of choice. It allows the maintenance of a constant degree of stress over a relatively long time period and it is least apt to cause artefactual distortion of the ballistocardiographic record.

If anoxemia is used as a test of cardiac function, it seems logical that the degree of stress induced should be made as standard as possible in all subjects. Since the degree of arterial desaturation reflects the degree of stress,[31] this would suggest that arterial oxygen saturation levels should be standard. It has been shown by Barach and co-workers,[42] Pruitt and associates,[24c] Houston,[43] Dripps and Comroe,[44] Penneys, Thomas and McLean[26] and others that the inhalation of a gas mixture of constant low oxygen content does not result in predictable oxygen saturation levels. Our work indicates that cardiovascular response to anoxemia is related directly to arterial oxygen saturation, and suggests that when physiologic variables are to be measured quantitatively, saturation should be controllable. The use of a gas mixture in which the oxygen content can be varied, combined with the use of an oximeter, supplies this need for control.

The advisability of using a method which permits the control of arterial oxygen saturation is demonstrated in our 2 patients who developed "positive" electrocardiographic changes and chest pain during the test. A positive response was produced in one (S. F.) at a saturation of 80 per cent while in the other (G. B.) the response was negative at 80 per cent but positive at 75 per cent saturation. These levels of saturation might not have been reached if a gas of fixed oxygen concentration, for instance 10 per cent oxygen, has been used, for the arterial oxygen saturation in the individual subject may be as high as 87 per cent when such a gas mixture is employed.[42] If positive responses are produced at different saturation levels[24f, 38] in patients with coronary artery disease, it would seem important to make sure that all test subjects attain the same degree of arterial desaturation before they be considered negative. This is relatively simple when a method is used which allows control of the level of arterial oxygen saturation.

Summary

1. Cardiovascular responses have been studied in 16 normal subjects and 11 patients with suspected coronary artery disease before, during and after the induction of oximetrically controlled anoxemia.

2. The physiologic variables studied were: (a) cardiac output, (b) pulse rate, (c) stroke volume, (d) left ventricular work, (e) maximum cardiac force per beat, (f) maximum cardiac force per minute, (g) mean blood pressure, (h) pulse pressure, (i) ballistocardiographic form and (j) electrocardiographic changes.

3. Progressive and significant increases occurred in cardiac output, pulse rate, left ventricular work, maximum cardiac force and pulse pressure during anoxemia in the normal subjects and in the 5 patients whose ballistocardiograms allowed the calculation of these variables. There were generally no significant differences between the two groups in such variables.

4. In the "normal group" at 70 per cent saturation, cardiac output increased 42.7 per cent, pulse rate increased 36.8 per cent, while stroke volume rose only 2.2 per cent; in the "patient group" these increases were 34.6 per cent, 28.4 per cent and 9.0 per cent, respectively. The increase in cardiac output at 70 per cent saturation was over twice as great in the normal women as in the normal men.

5. Two of the 11 patients had a positive electrocardiographic test for coronary insufficiency and in both chest pain was reproduced. No such findings occurred in the "normal group."

6. Control ballistocardiograms were all normal in form in the "normal group" and remained normal throughout the anoxemia test. In the "patient group" control ballistocardiograms were abnormal in 4, normal in 4 and borderline in 3. During anoxemia one normal, two borderline and one abnormal ballistocardiograms became abnormal or more abnormal.

7. There was no common physiologic response pattern in the patients who gave a positive electrocardiographic test, who developed chest pain during the test or who developed ballistocardiographic form abnormality.

8. It is suggested that the taking of ballistocardiograms and electrocardiograms during an anoxemia test may be of value in the diagnosis of coronary artery disease in the small percentage of cases where these two technics give

normal or equivocal results under resting conditions.

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Changes in Configuration of the Ventricular Chambers during the Cardiac Cycle

By ROBERT F. RUSHMER, M.D., AND DEAN K. CRYSTAL, M.D.

Cinefluorographic angiocardiography has been used to record the sequential changes in the size and shape of the right and left ventricular chambers and the external cardiac silhouette in dogs. Evidence is presented which indicates that (1) the left ventricle is usually filled more rapidly than it is emptied, (2) the diastolic size appears to remain remarkably constant during a major portion of the diastolic period and (3) residual blood remains within the ventricle at the end of systole.

CYCLIC changes in the size of the ventricles, the essential feature of cardiac function, have been widely studied by a variety of methods: (1) direct volumetric measurements by the plethysmographic technic, (2) analysis of arterial pulse waves, (3) roentgenkymography, (4) electrokymography and (5) indirect information concerning changes in stroke volume, gained from cardiac output determination by the Fick principle or ballistocardiography. The length of this list emphasizes the importance of information concerning the mechanism of ventricular contraction, and each method has certain advantages. Motion pictures of fluoroscopic images during angiocardiography present a combination of advantages not available in other methods. The size and the shape of the heart and of the individual chambers can be observed and measured during multiple cardiac cycles in the intact experimental animal. The presence of residual blood is readily detected in the ventricle. The sequence of events in the great vessels and heart can be related. Two disadvantages of this method are recognized: (1) the recorded images represent a two dimensional projection of the cavities, (2) rapid injection of radiopaque materials imposes an unusual load on the heart and circulation.

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METHODS

Cinefluorographic angiocardiography was performed on 20 dogs anesthetized with Nembutal and reclining in the left lateral position. The action was recorded with 16 mm. and 35 mm. cinefluorographic equipment.[1, 2,*] Diodrast† (25 cc. of a 70 per cent solution) was rapidly injected through indwelling needles or catheters secured in a jugular vein. Cinefluorographic recordings for 10 and 14 seconds provided an uninterrupted cinematic record of the opacified blood passing from the superior vena cava, through the heart and lungs and into the aorta. Eight films were exposed at a rate of 30 frames per second; the remainder at 15 frames per second. Various methods were used to extract information from the motion picture films: (1) repeated examination using motion picture projectors, (2) study of action and individual frames on film editing devices, (3) tracings of the projected images from film sequences, (4) photographic enlargement of strips of film and (5) a special motion picture printing technic termed "counter-offset" printing,[3] which is based on the following principle. In positive and negative copies of the original cinefluorographic film, the light areas in one correspond precisely with the dark areas in the other. If these two films are accurately superimposed in a printer, they partially neutralize or counteract each other, tending to produce a uniformly gray field. However, if the two counteracting films are superimposed with one film offset one frame in advance of the other, stationary structures remain subdued but the movement of a structure during the interval between frames appear as an area of markedly reduced density because in this area neutralization is less complete. Thus the time course of the move-

* The KX-1 X-ray Generator used in this study was provided by the General Electric X-ray Corporation.

† Diodrast was generously supplied for this project by the Winthrop-Stearns Company.

ment of radiopaque material may be followed on successive frames. In figure 4, the first series of four pictures (*A*-1, 2, 3, 4) corresponds to an original negative film. The second series (*B*-1, 2, 3, 4) was obtained by counter-offset printing. Some structural detail is visible because the density and contrast of the two superimposed films are not identical. However, in each frame, the leading edge of the Diodrast column moved into the dark areas on each frame during one-fifteenth second.

Results

Continuous cinefluorographic recording at 15 frames per second for 10 to 14 seconds produced 150 to 200 stages in the progression of the radiopaque substances from the superior vena cava to the descending aorta. The anatomic relations of the cardiac chambers in the dog are illustrated in Figure 1. The first portion (6.4 seconds) of a typical record is reproduced in figures 2 and 3. Diodrast approached and entered the right atrium during the eight frames in column *A* and the first five frames in column *B* (fig. 2). The auricular appendage was outlined between frames *B*-3 and *B*-7, the position of the tricuspid valves was clearly indicated in frames *B*-3, 4, 5, and retrograde flow into the azygos vein appeared in frames *B*-4, 5. In frame *B*-6 the tricuspid valves opened and opacified blood surged into the right ventricle. The first visible contraction of the right ventricle occurred between *C*-4 and *C*-8, filling the pulmonary arteries. Refilling of the right ventricle was largely complete within one-fifteenth second between *C*-8 and *D*-1. Retrograde flow into the inferior vena cava began during a diastolic period (*D*-3) (the next systole began in frame *D*-8). Since the diaphragm was rising at this time, the retrograde flow occurred during the expiratory phase of respiration, but this was not necessarily true in other cases. During the second right ventricular systole (*D*-8, *E*-1, 2, 3), Diodrast appeared in the left atrium only 1.3 seconds after initial right ventricular opacification. The systolic period occupied four frames (*C*-4, 5, 6, 7 and *D*-8, *E*-1, 2, 3) while filling of the chamber appeared complete within two frames (*C*-8, *D*-1, and *E*-4, 5). During the remainder of the diastolic period the right ventricular chamber was remarkably constant in size and shape even though the injection of Diodrast was forceful enough to produce retrograde flow for a considerable distance into the inferior vena cava. The left ventricular cavity became partially opacified during the final diastolic filling in figure 2 (frames *F*-7, 8).

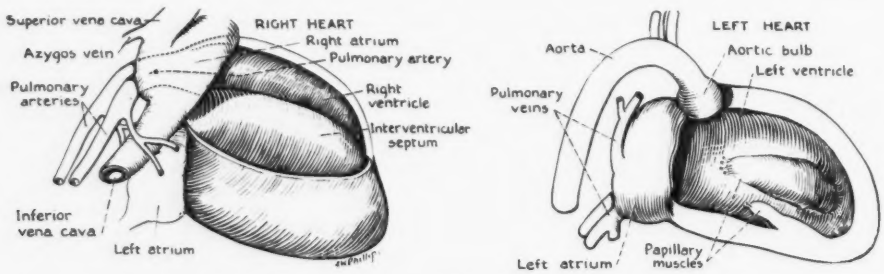

Fig. 1. The anatomic relations of the cardiac chambers and great vessels in the dog as reconstructed from the cinefluorographic films, supplemented by anatomic studies.

During the next three seconds, both ventricles were simultaneously opacified by the Diodrast (fig. 3). The interatrial and interventricular septa can be identified, separating the right and left atria and the two ventricles respectively (fig. 3, *J*-1–7). Between the left atrium and left ventricle, the location of the mitral valve appears in a number of pictures, particularly *H*-5, 6, 7, 8, and *K*-5, 6, 7, 8. As the right ventricle became cleared of Diodrast, the left heart chambers could be more readily distinguished. The thoracic aorta could be followed from the aortic bulb to the descending limb of the arch (fig. 2, frames *L*, 1–8). The rapidity of early diastolic filling (*L*-1, 2) of the left ventricle relative to the systolic period (*K*-4–7) is also evident in this series.

Right Ventricular Filling. Right ventricular

filling can best be studied during the initial entrance of Diodrast into that chamber. As the right atrium filled with radiopaque material during systole, the tricuspid valves became outlined at the atrioventricular junction (fig. 4, *A*-2, 3). The tricuspid valves inverted slightly into the right ventricle (fig. 4, *A*-2, 3) and gaped wide as blood gushed into the ventricular chamber (*A*-4). The progress of the Diodrast during each one-fifteenth second interval is indicated by the dark areas in the counter-offset print (fig. 4, *B*-1, 2, 3, 4).

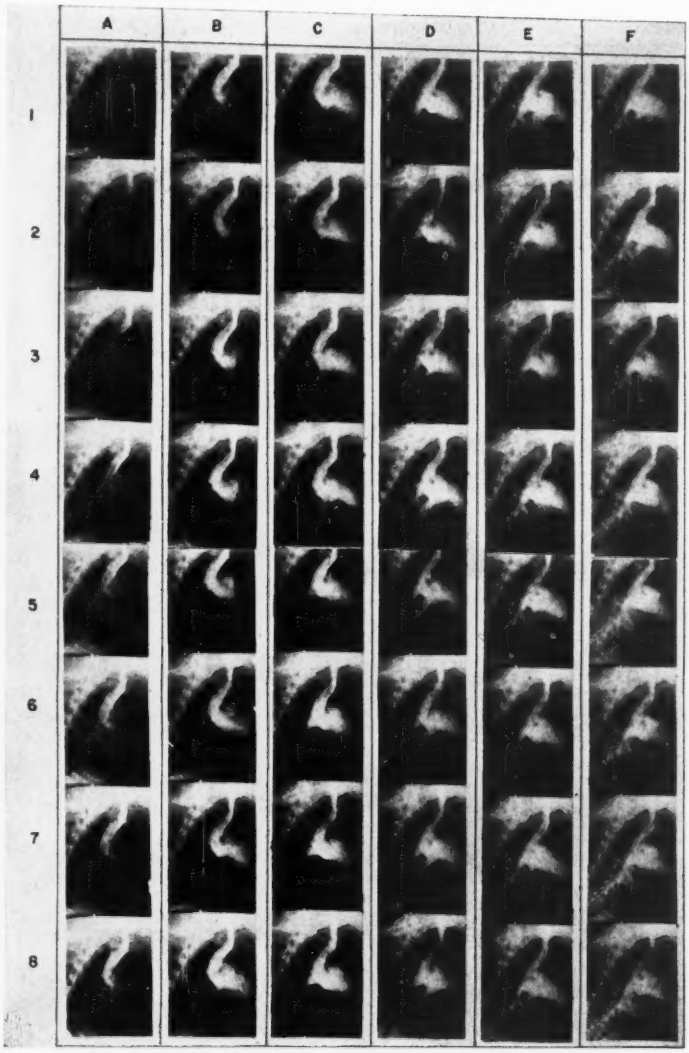

FIG. 2. Successive frames printed from a cinefluorographic film, exposed at 15 frames per second to illustrate the filling and contraction of the right atrium and ventricle during 3.2 seconds following the injection of contrast media.

Currents of flow within the ventricular chamber were frequently observed. In 3 animals, Lipiodal, characterized by its cohesion and immiscibility with blood, was injected in lieu of

Diodrast. In each case, the stream of Lipiodal executed a spiral movement as it entered the right ventricular chamber (fig. 4 *C*, *D*, *E*). motion imparted to the stream of Lipiodal. Currents of blood, reflected back toward the tricuspid valve (fig. 4, *E*-2) were frequently

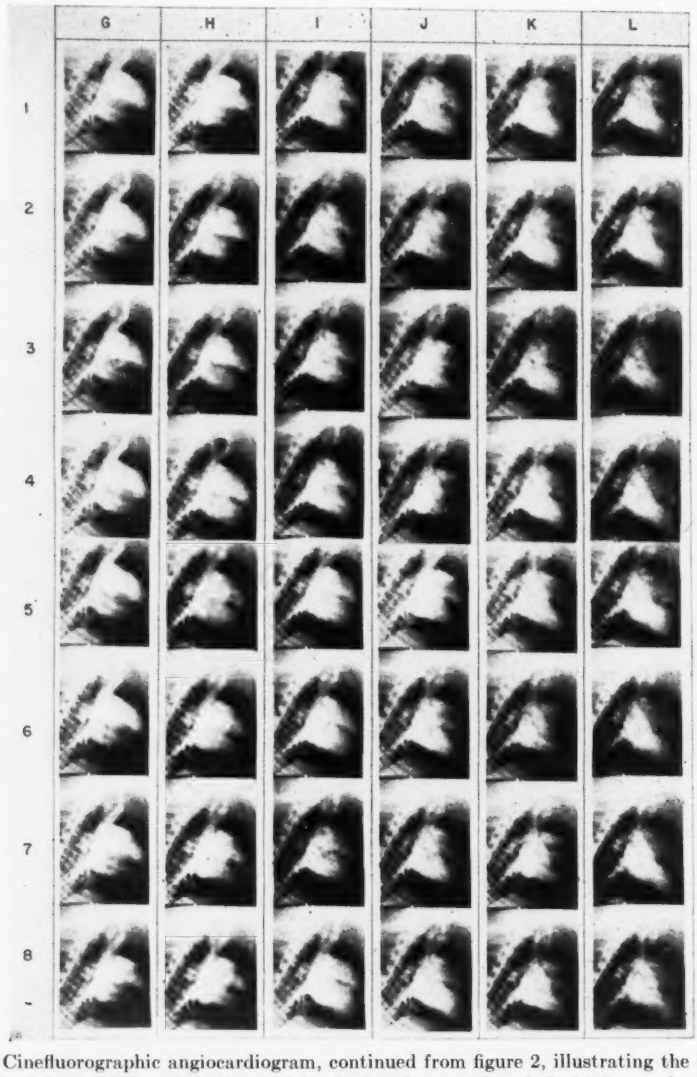

FIG. 3. Cinefluorographic angiocardiogram, continued from figure 2, illustrating the contraction of both the right and left atria and ventricles during the second period of 3.2 seconds.

A similar spiral pattern of Diodrast was noted in one case. The inferior vena cava enters the right atrium near the point at which the spiral configuration began (note arrows in *D*-1 and *E*-1). The inflow of blood from two convergent sources may be responsible for the swirling observed, but in each case they occurred well before the end of the diastolic period.

Right Ventricular Contraction. The right ventricle resembles a triangular pocket attached to the left ventricle along the interventricular septum. Bounded by the free wall of the right

ventricle and the bulging interventricular septum, the right ventricular chamber is concavo-convex (fig. 1). The distance between the septum and free wall is greatest along the inflow tract and becomes progressively less toward the periphery. When a low concentration of contrast media filled the chamber, the remarkably thin space between the opposing surfaces at the periphery of the ventricular cavity was readily penetrated by x-ray.

In one experiment, a rubber catheter, inserted through the right jugular vein into the right ventricle, outlined the lateral extent of the right ventricle (fig. 5). At the end of a diastolic period (fig. 5, *A*-2), Diodrast was fairly evenly distributed through the right ventricular chamber. During the succeeding systole (*A* 2, 3, 4 and *B*-1) compression of the lateral portions of the right ventricle cleared the region from the catheter to the central cavity and the pulmonary artery was rapidly filled (*B*-1). A branch of the pulmonary artery, filled with the same concentration of Diodrast that existed in the right ventricle, passed anteriorly over the heart shadow along a course roughly parallel to that of the catheter (fig. 5, *B*-1). It is apparent that the layer of blood in the peripheral portion of the right ventricle is little if any thicker than the diameter of the small branch of the pulmonary artery. Even during diastole, the opacity of the pulmonary branch is as great as most of the peripheral areas (fig. 5, *B*-3, 4 and *D*-3, 4). The configuration of the central portion of the right ventricular chamber is illustrated by a counter-offset print (fig. 5, *E*-1–4) in which the peripheral portions of the chamber do not obscure the pictures. The first three frames (*E*-1, 2, 3) reveal the systolic

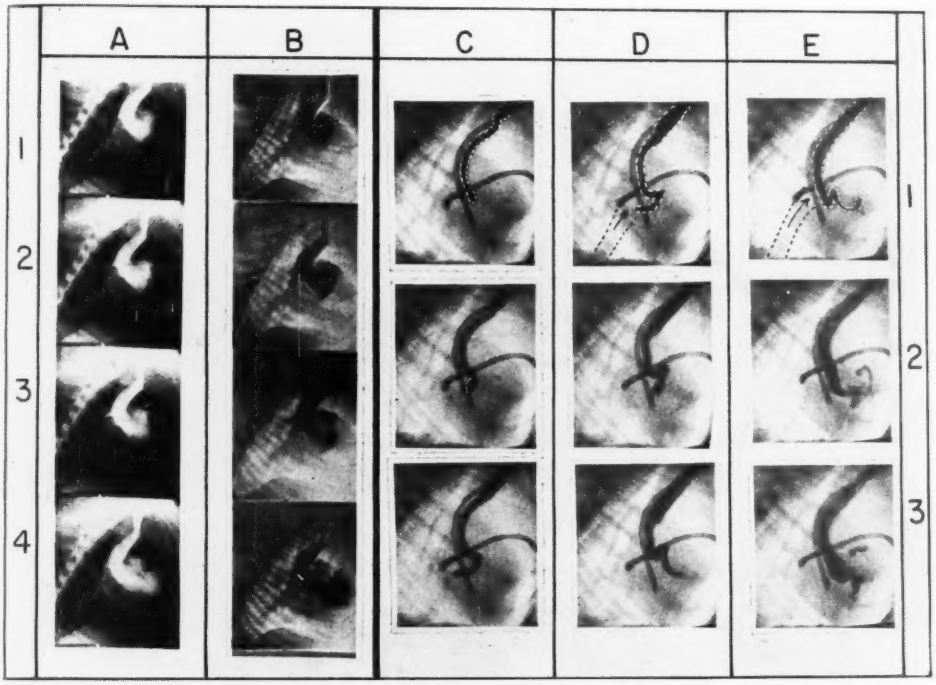

FIG. 4. *A*. Inversion of the tricuspid valves and initial filling of the right ventricle. *B*. Counter-offset print of the sequence in *A* to emphasize the progress of the contrast media in each frame (see text). *C*. Spiral currents of flow within the right ventricle during diastole are indicated by a streamer of iodized oil (outlined by interrupted white lines). Catheters for recording right and left atrial pressures also appear in the pictures.

size and the final frame (*E*-4) records the initial stage of diastole.

Left Ventricular Contraction. Since the contrast medium was diluted in the lungs, opacification of the left ventricle was gradual and left ventricular filling could not be adequately studied. In one animal with relative bradycardia, one cardiac cycle occupied twenty-four frames (fig. 6, *A*-1 to *F*-4). The change in capacity of the left ventricular cavity from atrial systole (fig. 6, *A*-1) to complete filling (fig. 6, *F*-4) represents only a small fraction of its total content. A large residual volume remained at the end of systole (*C*-4).

The left ventricular chamber is irregular in shape but most closely approximates a cylinder with a short conoid segment extending from one end (fig. 6). During left ventricular systole, a reduction in the capacity of the left ventricle could result from compression of the cross sectional diameter, from shortening of the chamber, or both. Marked narrowing and slight shortening of the ventricular cavity produced an unusual degree of systolic emptying in one experiment (fig. 3, *K*-6, 7). In another animal, a large residual ventricular volume remained at the end of systole (fig. 6, *C*-4) since the diameter of the chamber was reduced to a lesser degree and there was no visible change in length. In every case, left ventricular systole was characterized by a marked reduction in width and a relatively insignificant degree of shortening.

The aorta characteristically became narrow

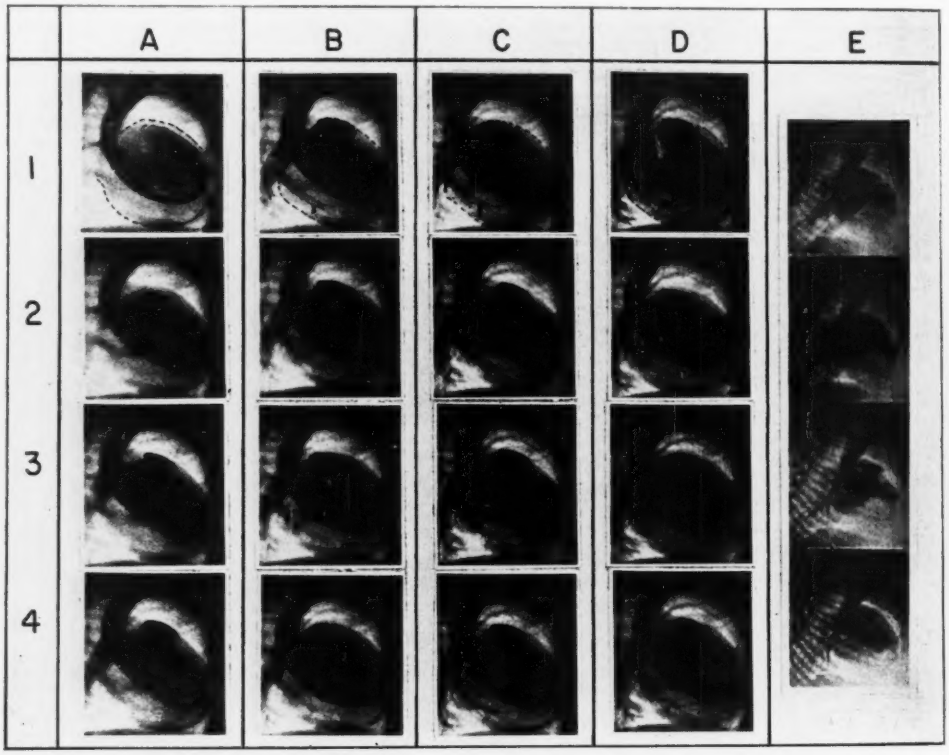

FIG. 5. Contraction of a right ventricle filled with diluted contrast media. A catheter outlines the peripheral extent of the right ventricular chamber. This ventricular chamber, the external surface of the free wall and a branch of the pulmonary artery are outlined. In *E*, the form of the central portion of the right ventricular chamber is emphasized by counter-offset printing.

during the diastolic run-off period, and the ascending limb of the aorta subtended a very acute angle with the long axis of the left ventricle (fig. 6, *A*-1). Left ventricular systole expanded the aorta (Fig. 6, *C*-1, *D*-1) while the angle between the ascending aorta and the left ventricle was increased (*D*-1). During projection this phenomenon produces a rocking motion of the ascending aorta which assumed a more nearly vertical position during each systole and inclined posteriorly during diastole. Rapid injection of blood from the ventricle apparently elongated the aorta elevating the arch. However, it is worth noting that, contrary to the principle of the Borden tube, the aortic arch assumed a greater curvature during periods when its luminal pressure was increased.

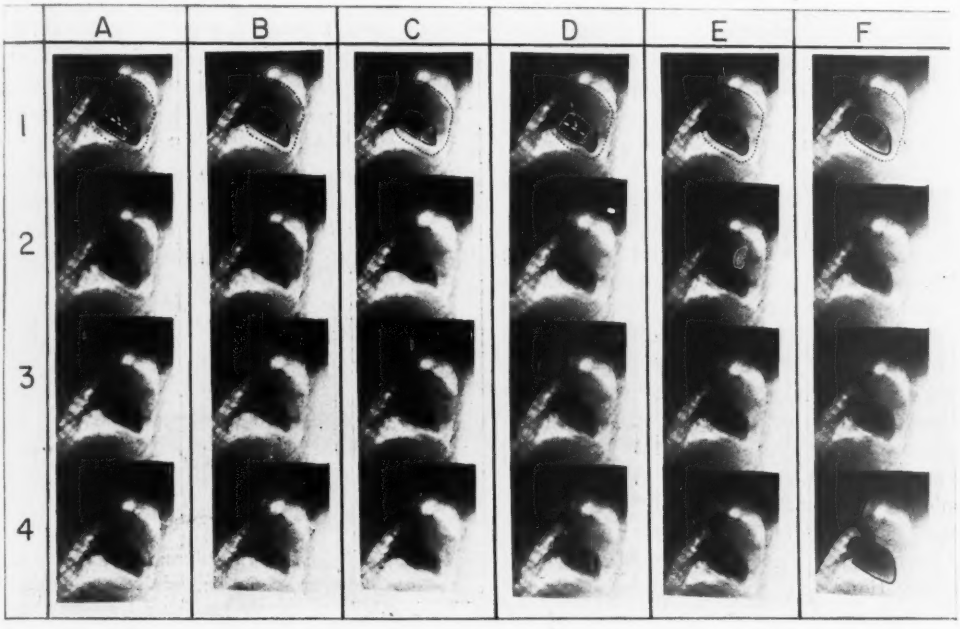

FIG. 6. Contraction of the left ventricle after the right ventricle is cleared of Diodrast. The angle subtended between the ascending aorta and the long axis of the ventricle is indicated in *A*-1 and *D*-1. (See fig. 1 for anatomic relations.)

DISCUSSION

The observation that diastolic filling of the ventricles occurs at a very rapid rate is not new. Henderson[4] in 1906 described plethysmographic recordings of the changes in ventricular volume as follows: "The rapidity of the inflow indicated by this rise of the volume curve is startling; for it shows that the refilling of the ventricles occurs early in diastole, and that it is as rapid a process as is the systolic emptying." He summarized the work of earlier investigators and pointed out that Luciani, obtaining similar records, had gone so far as to propose an active diastolic expanding force originating in the myocardium.

The retrograde flow of radiopaque material into the azygos and inferior vena cava is a consequence of the rapid injection of a fairly large quantity of fluid into the expansile venous system. The fact that retrograde flow into the inferior vena cava occurred while the apparent size of the right ventricle remained relatively constant supplies confirmatory evidence that, early in diastole, the chamber becomes rapidly filled to a point beyond which further distension is resisted by unknown factors. Since filling was virtually completed during the first third of a diastolic period at heart rates up to

180 per minute, the rate of diastolic filling is probably not the primary limiting factor in cardiac output produced by tachycardia under normal conditions. Stead and Warren,[5] reporting conditions under which changes in cardiac output occurred without corresponding changes in venous pressure, concluded that the venous pressure is normally more than adequate to produce ample filling of the ventricular chambers.

Judging by the cinefluorographic records, the configuration and contraction of the right and left ventricular chambers are very different. The right ventricle resembles a pocket fastened to the periphery of the convex intraventricular septum. During contraction, the free wall conforms more closely to the convex septum, ejecting blood into the pulmonary artery and at the same time evacuating most of the blood contained around the periphery of the chamber.

The left ventricle resembles a cylinder with a conoid segment at the apical end. Systole produces primarily a reduction in the diameter of the chamber. Shortening of the ventricle plays a minor role in the systolic ejection. It is generally stated that during systole the heart is rotated on its long axis. If this were true, the septal shadow separating the two ventricles would tend to become obscured by the opacified blood. There was no evidence for rotation of the heart in any case studied. The elongation and elevation of the aortic arch during systole is probably an expression of some of the forces recorded by the ballistocardiogram.

Conclusions

1. Angiocardiograms, recorded cinefluorographically, characteristically revealed a retrograde flow of opacified blood into the azygos vein, the inferior vena cava and occasionally into the opposite jugular vein, presumably due to the rapid injection of 25 cc. of radiopaque material.

2. As the right ventricle filled, currents of flow were generally observed. Lipiodal, injected in lieu of Diodrast, executed a spiral movement as it entered the ventricular chamber. Streams of blood from the superior and inferior vena cavae converging from different directions may underlie this finding.

3. The filling of both right and left ventricles occurred more quickly than systolic ejection. The area of the ventricular chambers appeared to remain relatively constant during the last two-thirds of diastole, even in the presence of retrograde flow into the inferior vena cava. This observation has been confirmed by planimetric measurements which will be described in a subsequent report.

4. Left ventricular contraction involved primarily a reduction in the width or diameter of the chamber. Shortening of the long axis of the ventricle played a minor role in systolic ejection.

5. During systole, the diameter of the aorta was markedly increased and the aortic arch became elevated and more acutely curved.

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The Mechanics of Ventricular Contraction
A Cinefluorographic Study

By Robert F. Rushmer, M.D., and Nathan Thal, M.D.

Linear and planimetric measurements have been made on tracings of the right and left ventricular chambers from successive motion picture frames, obtained by cinefluorographic angiocardiography in anesthetized dogs. At the end of systole, varying amounts of residual blood, some 35 per cent of the diastolic volume, remain in the chamber. Filling occurs more rapidly than ventricular ejection and is virtually completed in early diastole. The left ventricular chamber is reduced in size during systole primarily by a reduction in width rather than a shortening of the longitudinal axis. Increased stroke output was accomplished by three mechanisms: (1) increased emptying of the ventricle by progressive shortening of the ventricular chamber; (2) increased filling in early diastole; (3) increased filling in the presystolic period, persumably because the atrial contraction more effectively distended the ventricle. The mechanisms responsible for the systolic residual blood and the retardation of filling which occurs early in diastole are discussed in terms of the anatomy, geometry and functional characteristics of the ventricular myocardium. A comparison is made of the right and left ventricles with reference to their luminal pressure and fiber tension relationships.

THE circulation of opacified blood from the superior vena cava to the descending aorta, studied by means of cinematic fluorography, has been described in a previous report.[1] Examination and projection of the motion picture films indicated that (1) the ventricles fill more rapidly than they empty; (2) the projected areas of the two ventricles appeared to remain relatively constant after the rapid filling phase; (3) no significant change in ventricular size could be consistently observed during the presystolic period when atrial contraction occurs; (4) during systole, peripheral portions of the concavoconvex right ventricular chamber were almost completely evacuated; (5) the capacity of cylindrical left ventricular chamber was reduced during systole by reduction in diameter while longitudinal shortening was variable and of small degree; (6) the thickness of the ventricular walls increased during systole.

This communication deals with evidence concerning these points derived from linear and planimetric measurements from tracings of the right and left ventricular cavities. The changes in the size and configuration of the ventricular cavities, combined with their anatomic and geometric characteristics, has been related to the function and mechanics of right and left ventricular contraction.

Methods

Through indwelling catheters or needles, Diodrast* (25 cc. of 70 per cent solution) was rapidly injected into the right jugular veins in 20 dogs, positioned in the left lateral reclining position. Motion pictures recorded the sequence of events for periods of 10 to 14 seconds, using 16 and 35 mm. cinefluorographic equipment.[2, 3] Twelve films were selected for detailed study, of which eight had been exposed at 15 frames per second and four at 30 frames per second. Under the same conditions as obtained during the cinefluorographic angiocardiography, films were also taken of a circular brass plate positioned at the level of the dog's heart. By means of a strip film projector, the image of the brass plate on 35 mm. film was focused on a horizontal surface and the projection distance was varied until the circular image from the film coincided with the original brass plate. In this way, the projected image of the brass plate, and similarly the image of the heart, were accurately restored to natural size. For 16 mm. film, the projection distance was excessive, so smaller images from a standard distance were measured and corrected to natural

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* Generously supplied for this project by the Winthrop-Stearns Co.

size by factors computed from the real and projected dimensions of the brass plate.

The projected images of the right and left ventricular cavities and, whenever possible, the external cardiac silhouettes were traced on plain white paper. The walls of the left ventricular cavity could be drawn with confidence, particularly when the right ventricle had become cleared of contrast media. The locations of the mitral valves were not invariably distinguishable, so the basilar limits of the ventricles were delineated by straight lines connecting the valve roots, and across the root of the aorta. After establishing the limits of the chamber, the following measurements were made: (1) the left ventricular area using a planimeter, (2) the length of the ventricle from the midpoint of the mitral valve to the apex, (3) the width of the ventricle on a line perpendicular to the longitudinal axis at its midpoint (fig. 6*B*). The area, length and width of the external cardiac silhouette were also measured when possible.

The anterior or free wall of the right ventricle is concave and the septal wall is convex, so the peripheral extensions of the right ventricular chamber are tapered and difficult to distinguish. The shape of the central portion of the chamber could be measured only during cycles in which concentration of the contrast medium was sufficiently low (fig. 1). Because of the complex shape of the right ventricle and the inherent difficulties involved in producing reliable tracings, the following measurements were performed in only 3 selected cases: (1) the area bounded by the tricuspid valve roots, the septal dome and the free wall of the ventricle, (2) the length of the right ventricular chamber from the level of the tricuspid valve to the apex on a line bisecting the cardiac silhouette, and (3) the width of the right ventricle on a line perpendicular to the long dimension at its midpoint (fig. 6*B*).

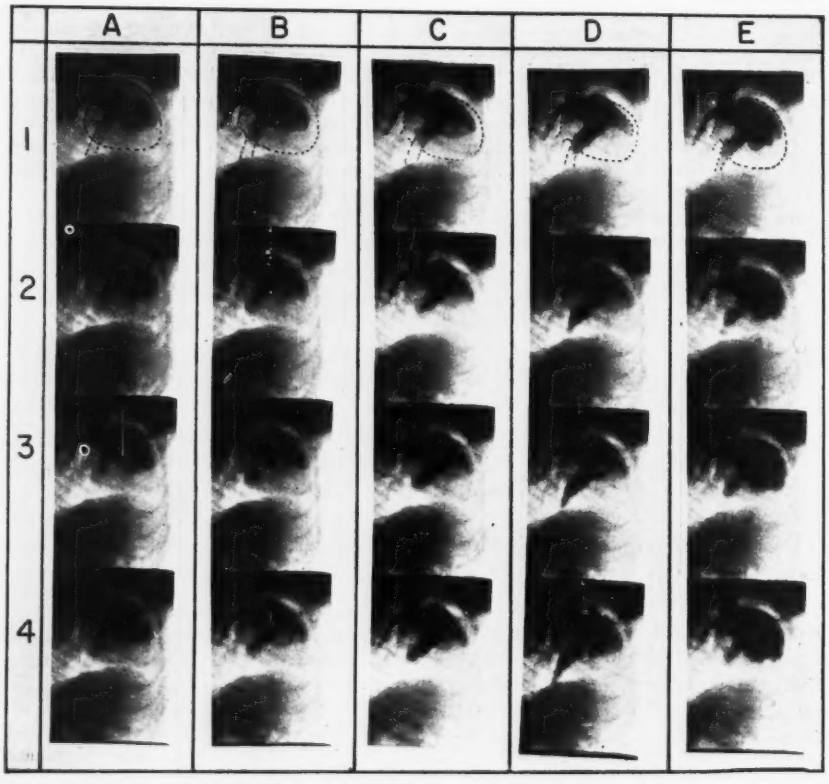

FIG. 1. Contraction of the right ventricle filled with a low concentration of Diodrast, photographed at 30 frames per second. Systole begins in *B*-2, and is complete in *D*-2. Filling is virtually complete in *E*-2.

To study the three dimensional configuration of the ventricular chambers in relation to the projected images, casts of freshly excised hearts were produced. An initial attempt, using agar to reproduce the chambers, was unsuccessful because the myocardium gradually became distended before setting

was complete. This difficulty was circumvented as follows: With the animal on artificial respiration, the superior and inferior venae cavae were clamped through a wide thoracotomy. After a few beats, the heart became virtually empty and the remaining inflow and outflow vessels were also quickly clamped. The heart was excised and washed, and the left ventricle was immediately filled with special dental perfection plaster (D.P.) while the heart continued to contract vigorously. The plaster hardened within one minute and fibrillary contractions of the myocardium persisted while a similar cast was made of the right ventricle. These casts appeared to reproduce accurately the form of the ventricular chambers observed on cinefluorographic records of the same animals.

Results

Photographic prints from sequential motion picture frames illustrate the sequence of events during right ventricular contraction. In one experiment, photographed on 16 mm. film at 30 frames per second, the right ventricle was filled with blood having a low concentration of Diodrast during one cycle (fig. 1). The low density band just below the level of the tricuspid valve suggests that the last increment of blood entered the ventricular chamber from the inferior vena cava (fig. 1*A*-1, 2, 3). As systole began (fig. 1*B*-1), the Diodrast became evenly dispersed. The free wall of the right ventricle was drawn toward the convex septal wall, and the lateral portions of the chamber, extending toward the center of the cardiac silhouette (*C*-1), became progressively cleared of opacified blood, leaving a narrow shadow extending from the valves to the apex (*D*-1). This narrow shadow represents the form of a sagittal section through the central portion of the right ventricular cavity. The peripheral extent of the right ventricular cavity is more clearly revealed during the succeeding diastolic interval (fig. 1*E*-1, 2, 3, 4). However, as the entire chamber became completely opaque, the central chamber became obscured. Comparing frames *C*-1 and *E*-1, the free wall of the right ventricle obviously increased in thickness during systole.

The anatomic basis for partial or complete obliteration of the tapered peripheral extensions of the right ventricle was provided by reconstructions of the heart from the angiocardiographic studies, supplemented by plaster casts of the ventricular chambers (fig. 2*A*). A cross sectional view of the ventricles near the base reveals a large right ventricular inflow tract on the right and the pulmonary conus region of the left. A section approximately halfway from base to apex emphasizes the crescentic shape of the right ventricular chamber. The change in right ventricular configuration from diastole to systole is suggested diagrammatically (fig. 2*B*). Obliteration of the peripheral portions of the chamber is represented as due to an increased bulging of the interventricular septum coupled with contraction of the free wall. The spiral course of the superficial muscles[4, 5, 6] and the circumferential arrangement of the deep muscle layers as illustrated by the deep bulbospiral muscle[4] are indicated in figure 2*C*.

Left ventricular contraction was associated with a marked reduction in the width, and a relatively insignificant reduction in length. This point is strikingly illustrated in one experiment photographed at 30 frames per second (fig. 3). A more accurate appraisal of the changes in ventricular size was obtained by planimetric measurements of the projected image of the left ventricular chamber (fig. 4). The sequential changes in ventricular area, measured from films taken at 15 and 30 frames per second, were plotted on the same time scale (fig. 5). Three cycles from each of two experiments have been superimposed to indicate the degree of reproducibility of the recorded areas (fig. 5*A*). The initial rate of reduction in area during systole is rapid, slowing as contraction progresses to completion. However, during the first portion of diastole, the increase in size generally occurred at a more rapid rate than the corresponding phase of systole. In many instances, filling was complete within 0.13 second. A slight increase in area was frequently observed during auricular contraction in the presystolic period. In figure 5*B*, four cycles from one dog (interrupted lines) are compared with three cycles from another animal in which a progressive increase in the ventricular size occurred during successive presystolic periods (solid lines). This animal had received one injection of contrast media 20 minutes previously and died within 5 minutes after this, the second, injection.

Gross examination of the heart revealed only extreme dilation. In only two other films was there a significant increase in area during the presystolic period.

The changes in ventricular dimensions were measured in one animal with bradycardia of unknown origin (fig. 5*C*). The cycle length was 1.23 seconds (heart rate 48 per minute). During the diastolic interval, the recorded values were quite variable. The systolic reduction in the total area of both ventricles was only slightly greater than that of the left ventricle alone. This is consistent with the very small reduction in width of the right ventricle (fig. 5*D*). The initial reduction in the left ventricular area was associated with a diminished diameter, followed closely by a reduction in length, of the ventricular chamber (fig. 5*C*). As the width began to increase, the ventricular area continued to diminish due to continued shortening of the ventricle. This temporal relation between the lateral and longitudinal dimensions during contractions was not characteristic of all cases.

In one series of four left ventricular contractions, the stroke volume increased progressively (fig. 5*E*). The diastolic area increased and the systolic area became progressively reduced. The reduction in systolic area was accomplished almost exclusively by an increased degree of shortening, the width of the ventricle remaining remarkably constant at both systolic and diastolic levels. In several experiments, no progressive increase in the stroke volume was indicated by changes in ventricular area (fig. 5*A*).

The left ventricular wall was universally thicker during systole than during diastole (fig. 3). This observation led to a consideration of the geometric characteristics of the left ventricular wall. The left ventricle may be considered as a thick walled cylinder with a short conoid segment at the apex (fig. 6*A*). An increase in wall thickness during systole suggests that the radius of the inner layer of the ventricular wall was reduced more than the radius of the external surface of the ventricle. The differential changes in the radius and circum-

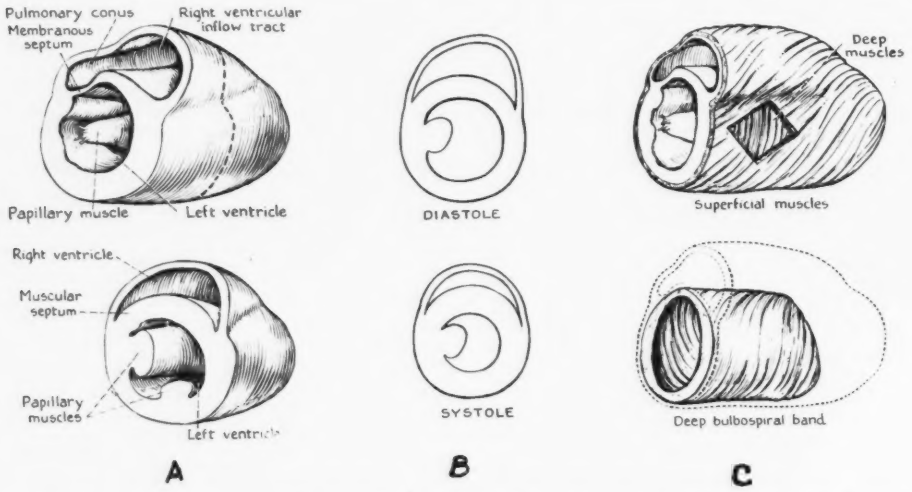

FIG. 2. *A*. Reconstruction of the ventricle chambers derived from cinefluorographic films supplemented by casts of freshly excised hearts. *B*. Changes in configuration of the ventricular chambers during systole (schematic). Note apposition of the peripheral portions of the septum and free wall of right ventricle. *C*. The superficial bulbospiral and sinuspiral muscles pursue a spiral course to the vortex (after Sabotta[6]). The deep bulbospiral bundle is representative of the deep left ventricle muscles in which the fibers tend to describe a circumferential arrangement in a cylindrical form (from Mall[4] and Robb and Robb[5]).

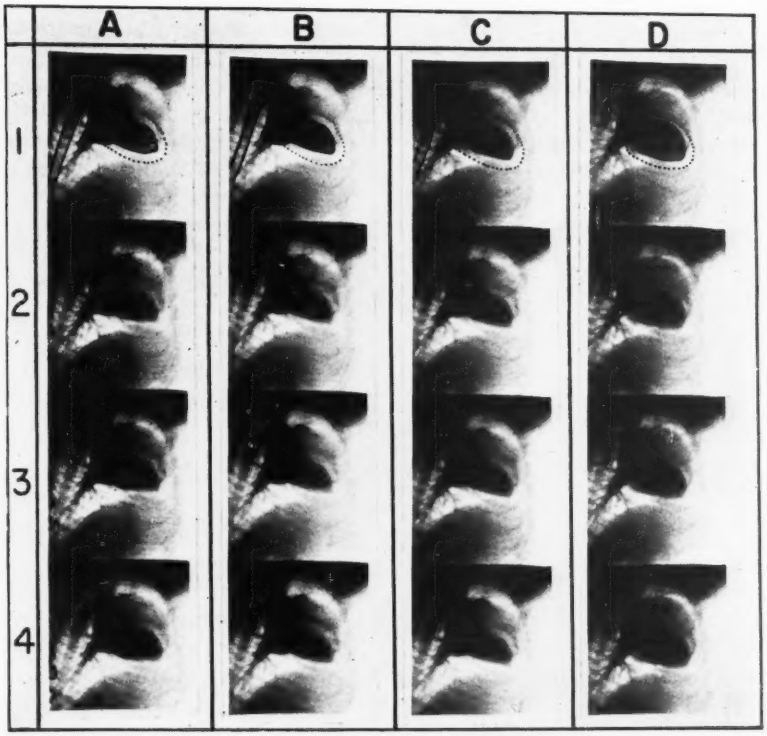

FIG. 3. The size and shape of the left ventricular chamber and the increase in wall thickness during systole indicated on films photographed at 30 frames per second. Systole begins in *A*-4 and is complete in *C*-4. The ventricular area is markedly increased during the next diastolic period (*D*-1, 2, 3, 4).

ference of the inner and outer layers of ventricular muscle may be analyzed in a thin cross section through the base of the left ventricle (fig. 6*A*). During systole the diameter of the left ventricular chamber was reduced from 3.8 cm. to 2.8 cm. in one case (fig. 5*C*) and from an average of 2.5 cm. to 1.4 cm. in another (fig. 5*E*). Due to the variability in heart size in different animals, the radius of the inner and outer cylinders during systole and diastole and the changes in volume of the internal and external cylindrical segments (fig. 6) are expressed in per cent of r_D and V_D,* respectively. Thus on the average $r_S = 0.6\, r_D$, and $V_S = 0.36\, V_D$. The thickness of the ventricular muscle was approximately 30 per cent of the ventricular radius (fig. 3). Therefore, $r_{D'} = 1.3\, r_D$ and $V_{D'} = 1.69\, V_I$ However, if the wall thickness remained the same during systole, the radius of the outer

FIG. 4. An enlargement of a single frame of a motion picture which illustrates the configuration of the left ventricle and the external borders of the ventricular musculature.

* The meaning of these and following symbols is shown in figure 6.

cylinder would be reduced by the same amount as the inner cylinder and $r_{S'} = 9r_D$ and $V_{S'} = .81\ V_D$. Under these conditions the systolic change in volume of the inner cylinder (ventricular chamber) would be $0.64\ V_D$ and the outer cylinder (chamber plus ventricular wall) would be $0.88\ V_D$. Thus the ventricular wall would be reduced in volume by an amount equal to 24 per cent of the initial diastolic volume of the ventricular chamber ($0.88\ V_{D'} - 0.64\ V_{D'}$). On the contrary, the radius of the external shell is reduced by a smaller amount than the internal cylinder so the ventricular wall thickness increases. Assuming that the mass of ventricular muscle is unchanged and that the quantity of blood expressed from the coronary circulation is negligible, the change in total volume of the external and internal cylindrical segments would be identical: ($V_{D'} - V_{S'} = V_D - V_S$). Under these conditions $V_{S'} = 1.05\ V_D$ and $r_{S'} = 1.03\ r_D$. The radius of the external cylinder would diminish 21 per cent while that of the inner cylinder would be reduced 40 per cent during ventricular systole. This explanation clarifies the observed increase in wall thickness, and it also indicates that the amount of shortening of myocardial fibers must vary in different layers of circumferentially

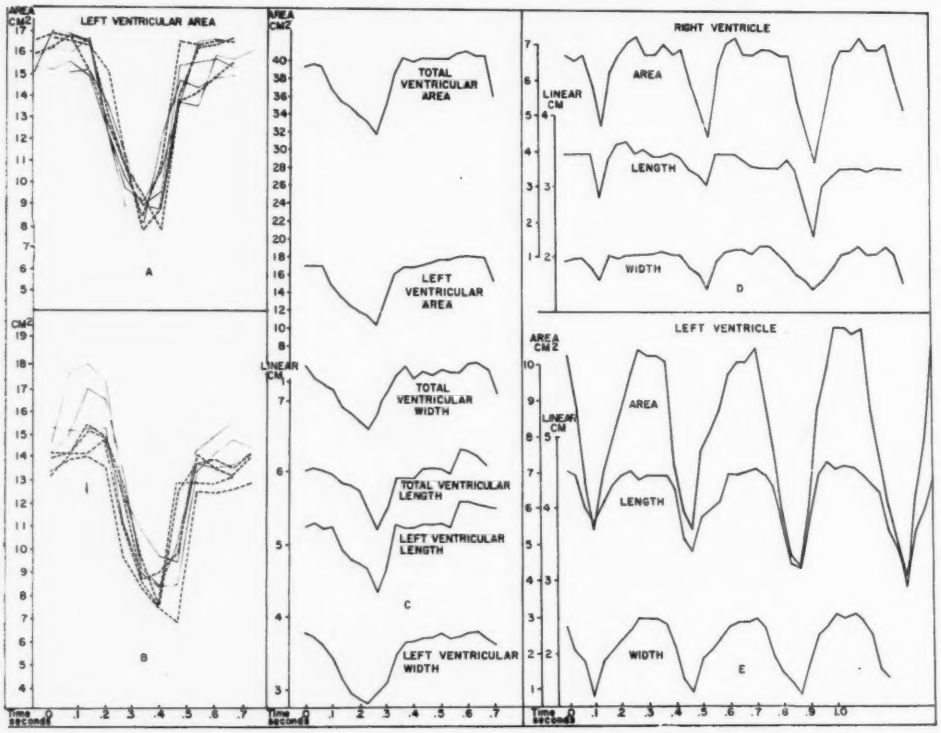

FIG. 5. *A*. The change in left ventricular area during three successive systoles from 2 different dogs. Note the rapid filling immediately after each systole. *B*. Progressive increase in diastolic filling in the presystolic period in a dog which died five minutes later (solid lines) is compared with four systoles from another experiment (interrupted lines) with a more typical pattern. *C*. The changes in ventricular dimensions in a dog with bradycardia (heart rate 48 per minute). The measurements were made as indicated in figure 6. *D*. Changes in the dimensions of the central portion of the right ventricular chamber. *E*. The changes in left ventricular dimensions during progressive increase in stroke volume (same experiment as *D*). Note that the increased filling and emptying are accomplished by changes in length, not width.

arranged ventricular muscle fibers. Most of the left ventricular wall in the basilar regions is composed of the deep bulbospiral and deep sinuspiral muscle layers[4] in which the fibers tend to be arranged around the circumference of the cylindrical segment (fig. 2*C*). Since the circumference of a circle is directly proportional to the radius, the percentage shortening of the inner layer of fibers must be greater than that of the outer layers ($C_D - C_S > C_{D'} - C_{S'}$). As a matter of fact, using the values obtained above, the fibers in the outer layer shorten by approximately 20 per cent while those in the inner layer shorten 40 per cent (see below).

If the conoid segment at the apex of the left ventricle were considered as a cone with a radius r_D, and a length equal to one-half the length of the cylindrical portion of the left ventricle (fig. 6*A*), the apical cone would contain an additional volume equal to only 17 per cent of the diastolic volume of the remainder of the ventricle. If, during systole, the radius of the cone were reduced by the same amount as the cylindrical portion of the ventricle (for example, to 0.6 r_D) the volume of the cone would be reduced to 0.06 V_D, if no ventricular shortening occurred.

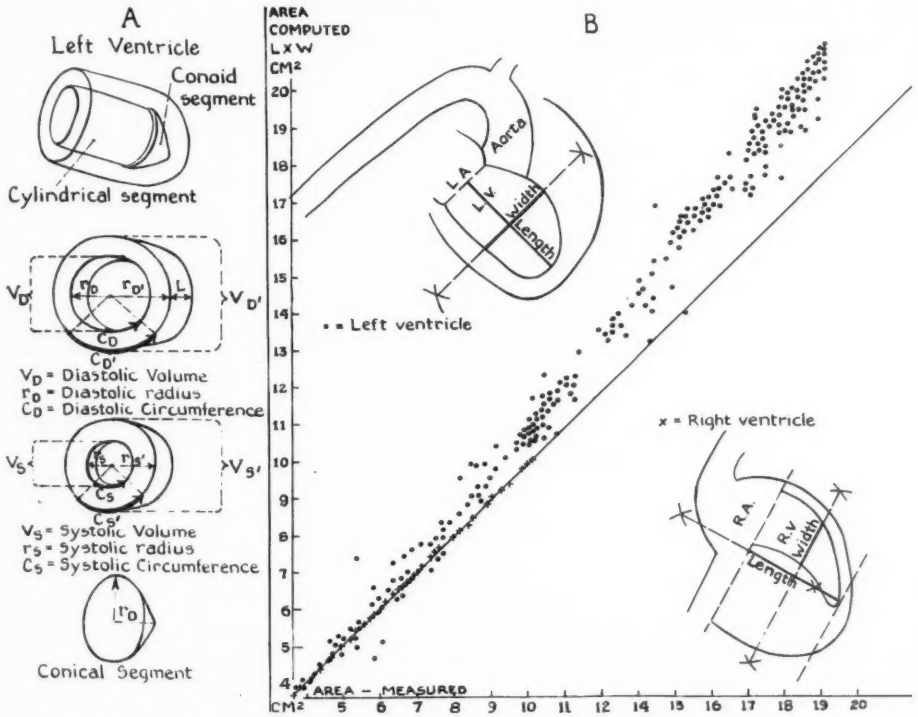

FIG. 6. *A*. The configuration of the left ventricle simplified for geometrical analysis (see text). *B*. The relation of the area, computed as the product of length and width, to the planimetrically measured area in each tracing indicates the reproducibility of the measurements. The sketches indicate the method of measuring length and width of the two ventricles.

Since the data derived from linear and planimetric measurements of the projected left ventricular chambers have been the principle source of information in this investigation, the reliability and reproducibility of the determinations were checked by plotting ventricular areas obtained in two different ways from 270 tracings. The length, width and area of the right and left ventricles were measured on ventricular tracings from 4 different animals in accordance with the methods indicated in the sample

tracings (fig. 6*B*). The product of ventricular length and width was plotted against the planimetrically measured area. If the two areas were identical in every case, all points would lie on a line with a 45 degree slope (coefficient of regression = 1.0). Despite the fact that a product of length times width described a rectangular area, the computed area was closely related to the measured area over a wide spread of values obtained by including data from systolic and diastolic intervals in dogs of varying size. As might be expected, the computed areas of the left ventricle were almost invariably greater than the measured areas. Similar measurements of right ventricular areas were plotted on the same graph (fig. 6*B*). The points fell with remarkable regularity along the line representing a regression coefficient of 1.0. It should be pointed out that a different relationship for both ventricles would have been obtained had the width been measured at any other level. The close relation obtained for the right ventricle may be attributed, in part, to the fact that the width at the midpoint of the ventricle was an average of the widths above and below this point.

Discussion

In the course of this investigation, three mechanisms for increasing stroke volume were encountered: (1) the diastolic volume may be augmented by increased filling in early diastole (fig. 5*E*); (2) more complete systolic emptying may occur with a corresponding reduction in the quantity of residual blood (fig. 5*E*); (3) the effectiveness of atrial contraction may be augmented by unknown factors to produce progressively increased diastolic filling in the presystolic interval (fig. 5*B*). The contribution by atrial systole was observed in 3 animals, one of which died spontaneously shortly after the angiocardiography. It should be noted that no progressive change in diastolic and systolic area was demonstrated in some of the experiments (fig. 5*A* and 5*B*, interrupted lines).

During systole, the projected area of the ventricular chambers diminished rapidly at first, tending to empty at a slower rate as the contraction neared completion. In every case, considerable quantities of blood remained in the ventricle at the end of systole. Early in diastole, the ventricular area increased, even more rapidly than it had been reduced during systole, and tended to reach a plateau which was sustained until the succeeding systole. However, neither the diastolic size nor the systolic size was fixed; progressive changes occurred at both extremes in successive cycles in certain animals. It seems essential that consideration be given to mechanisms which might determine the diastolic and systolic size of the ventricle.

Lundin[7] obtained length-tension curves from small bundles of myocardium isolated from frog hearts and reached the following conclusions: (1) The high viscosity of cardiac muscle facilitates filling of the heart because it permits the diastolic pressure to fall to zero even when the ventricle is dilated. (2) Further, the viscous properties of the myocardium oppose a rapid stretch with a marked increase in tension. Judging by the characteristics of isolated myocardial bundles, it would appear that both initial rapid inflow and abrupt termination of filling may be related to viscosity, a property which is more prominent in cardiac than in skeletal muscle. In contrast with these findings on isolated myocardial strips, Ramsey[8] summarized evidence from the intact frog heart as follows: "Normally, the greatest reversible dilation of the heart is reached when the cardiac fibers are at their rest length and exerting maximum tension or return." The definition of resting length in a ventricle composed of laminated strips of myocardial tissue, arranged circumferentially in a cylinder appears somewhat obscure, since any change in ventricular volume is accompanied by a greater change in length of the inner layers than of the outer layers of muscle. However, if a "resting" size of the ventricle exists, beyond which further distension involves a progressive increase in effective filling pressure, the diastolic plateau could be at least partially explained.

Just as the ventricles are restrained from distending as much as they are capable, ventricular systole fails to empty the chamber completely. Due to the space occupied by the papillary muscles (fig. 2) this residual volume is less than is indicated by the projected areas

of the ventricles. At least three mechanisms may tend to limit the degree of ventricular emptying during systole. Cardiac muscle builds up tension very rapidly and effectively under isometric conditions, but if the muscle is allowed to shorten during contraction, the tension falls off rather sharply.[7] Ejection of blood from the heart requires shortening of the fibers. Thus, the rate of ejection in early systole should be greater than late in systole (fig. 5). Secondly, the pressure in a viscus is related to the tension in the muscular components of the wall as follows: $P = \frac{2T}{R}$ where P is luminal pressure, T is muscular tension and R is the radius of the circle described by the muscle fibers. It is obvious that the muscles of the inner shell would contribute more to the luminal pressure than the outer layers, if all fibers exerted the same tension. However, evidence has been presented that, when the volume of the ventricle is reduced to 35 per cent of the diastolic volume, the circumference of the fibers comprising the inner wall of the left ventricle may be reduced by 40 per cent, while the outer fibers shorten about 21 per cent. It is possible that when contracton begins, the inner fibers are most effective in raising intraluminal pressure, but, as shortening progresses, the burden falls progressively more on the outer shells. Indeed, it is conceivable that near the end of contraction, the inner fibers contribute little or nothing and the outer fibers actually expend useless energy producing deformation or wrinkling of the inner laminations. Finally, more than 60 per cent of the blood in the left ventricle is ejected (considering the displacement of papillary muscles) when the radius is reduced only by 40 per cent of the diastolic circumference and further contraction becomes progressively less effective with respect to the volume expelled per unit shortening of the muscle fibers.

The cylindrical shape of the left ventricle is consistent with its function as a high pressure pump. When high pressures develop in the lumen of any hollow viscus, the shape of that viscus tends to approach a cylinder or a sphere. A sphere contains a greater volume per unit surface area than any other geometric configuration. Evidence was presented (fig. 5*E*) that the change in diameter of the cylindrical segment of the left ventricle was relatively constant and further change in area of the left ventricular silhouette was accomplished by increased shortening. It is tempting to speculate that reduction in width was due primarily to the action of the deep muscle layers with small circumference while the shortening was accomplished by the spirally arranged superficial muscles.

On the contrary, the right ventricle is bounded by a free wall which represents a segment of a sphere with a very large radius. The bulging of the septum into the ventricular chamber produces a configuration which is the antithesis of a high pressure region. With respect to the formula $P = \frac{2T}{R}$, the tension in the fibers of the right ventricular wall would be extremely high in order to produce pressures corresponding to those in the left ventricle. On the other hand, this architecture is particularly suited to large changes in capacity in the presence of low inflow and outflow pressures. This may explain the following clinical observations: (1) The lower pressure required for diastolic filling of the right ventricle may account for the fact that, normally, the right atrial pressure is lower than the left. (2) The right ventricle is vulnerable to increased outflow pressure. (3) In the fetal heart, where the outflow pressures of the two ventricles are approximately equal, the shape of the right ventricular chamber more closely resembles that of the left ventricle. (4) In the adult, compensation to increased outflow pressures involves distension of the right ventricular chamber to a more spherical configuration.

Conclusions

1. The initial filling of the ventricles occurs more rapidly than the ejection during systole. In most cases, filling was completed early in diastole and the ventricular size (area) remained remarkably constant until the succeeding systole. In general, atrial contraction produced little change in the diastolic size of the ventricular cavities

2. The right ventricular area is bounded by

the concave surface of the free wall and the convex surface of the septum, producing a semilunar configuration in cross section. During contraction, the blood in lateral folds of the ventricle was evacuated, apparently leaving a potential space between the septum and the free wall, in certain areas.

3. The left ventricle most closely resembles a cylinder extended at one end into a conoid segment. Left ventricular systole involves primarily a reduction in the diameter, supplemented by a relatively small reduction in length of the chamber. Judging from the laminated arrangement of myocardial sheets, the reduction in width may be due to the deep muscle components while the shortening is produced by the superficial layers.

4. The wall thickness of both ventricles increases during systole, an observation which is explained on the basis that for any particular change in volume, the circumference (and radius) of the inner layer of myocardial fibers is affected more than that of the outer shell. The fact that the ventricular size remains relatively constant during a major portion of the diastolic period has been discussed in terms of the "viscosity" of the cardiac fibers as described by Lundin.[7]

5. The presence of residual blood in the ventricles at the end of systole has been discussed in terms of (1) the rapid loss in tension of myocardial fibers during shortening, (2) the changes in the fiber length in the inner and outer layers of muscle and (3) the energy expenditure required to completely evacuate the chamber.

6. The area of the left ventricle, computed as the product of length times width, bears a close relationship to the area measured planimetrically.

7. The right ventricle is architecturally suited to great lability in stroke volume if the outflow pressure remains low. It is correspondingly vulnerable to increased outflow pressures. The left ventricle is adapted for ejection against a high outflow pressure. The relation of the different characteristics of the two ventricles was discussed in terms of common clinical observations.

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The Effect of Amytal on the Cardiac Output and Peripheral Resistance of Man

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Measurements of cardiac output and intra-arterial pressure on 5 normal young men and 5 hypertensive patients before and during sedation with Amytal demonstrated a decreased cardiac output and an increased peripheral resistance during the period of sedation. It is concluded that the theoretic basis for the use of Amytal sedation as a device for selection of hypertensive patients for sympathectomy is not valid.

AMYTAL, particularly its sodium salt, is known to cause a reduction in the blood pressure of some hypertensive patients. It has been assumed that the drug owes its hypotensive effect to a reduction in peripheral resistance and on this basis a Sodium Amytal test has been devised to aid in the selection of hypertensive patients for dorsolumbar sympathectomy.[1, 2] Proof that the drug acts specifically to reduce the peripheral resistance is, however, lacking. Since the level of the mean blood pressure is determined by the output of the heart as well as the total peripheral resistance, it is clearly necessary to measure all three factors simultaneously in order to discern the hemodynamic action of the drug. The following experiments were designed to test existing assumptions concerning the hemodynamic action of Sodium Amytal.

METHODS

Ballistocardiograms, recordings of the heart sounds, and femoral arterial pressure tracings were made simultaneously before and after the administration of Sodium Amytal to normal and hypertensive subjects. The ballistocardiograph was a low frequency, critically damped instrument of the type described by Nickerson, Warren, and Brannon.[3] A strain gage and a no. 18 Cournand needle were used to record the femoral pressure. Suitable hydrostatic dampers were introduced into the blood pressure recording system so that the complete recording system would pass an instantaneous square wave of 250 mm. Hg pressure with a 5 per cent overshoot. Static calibrations were carried out with a mercury manometer after every measurement of pressure. Between actual recordings the intra-arterial needle was disconnected from the strain gage and a stylet was placed in the lumen to prevent clotting.

Values for the stroke volume were determined according to the formula of Nickerson[3] and the cardiac output was calculated in terms of liters per minute; ten cycles were measured for each estimation of the output. The mean blood pressure was obtained by planimetric integration of the area under the pulse wave tracing. The total peripheral resistance in dynes cm.$^{-5}$ seconds was then calculated by dividing the mean blood pressure in mm. Hg by the cardiac output in cc. per second and multiplying by the factor 1332.

The subjects were 5 normotensive men between 19 and 25 years of age, and 5 men, aged between 34 and 40 years, who had essential hypertension. The mean surface areas of the two groups were 1.94 and 1.87 square meters, respectively.

Every effort was made to carry out the procedure under rigidly controlled conditions. The subjects reported to the laboratory late in the afternoon without having eaten lunch. They were placed on the ballistocardiograph table on an air mattress which was inflated during the insertion of the needle in the femoral artery and between periods of observation but which was deflated during actual observations. The temperature of the room was maintained at 24.5 ± 0.5 C., with the humidity at 50 per cent relative saturation. After the control observations were obtained, the subject received 0.40 Gm. of Sodium Amytal by mouth. An additional dose of 0.20 Gm. was given an hour later. This procedure was not followed in the case of patient G where the second and third doses were 0.4 Gm. each. This increased dosage was employed because G was known to have an increased tolerance for the drug.

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TABLE 1.—*The Stroke Volume in Cubic Centimeters and the Cardiac Output in Liters per Minute of Five Normotensive and Five Hypertensive Men before and during Four Hours of Sedation with Sodium Amytal*

Subject	Stroke Volume, cc.					Cardiac Output, L./min.				
	Hours after First Dose					Hours after First Dose				
	Control	1	2	3	4	Control	1	2	3	4
Normotensive										
A	131	85	100	92	80	10.35	6.21	7.50	6.90	5.84
B	123	117	83	119	144	7.75	5.24	4.48	6.90	9.51
C	117	98	91	84	75	7.37	6.27	5.46	5.38	5.33
D	118	112	124	99	119	7.43	6.94	9.55	6.83	7.85
E	124	90	87	100	96	7.44	5.40	4.87	5.80	5.18
Mean	123	96	97	99	102	8.07	6.01	6.37	6.36	6.74
Hypertensive										
F	92	75	63	72	65	6.72	5.34	3.80	4.88	4.17
G	71	78	75			6.63	7.36	6.23		
H	44	52	36	36		3.56	4.11	2.99	3.06	
I	86	71	49			6.28	5.04	3.33		
J	88	65	73	71	43	5.90	4.75	4.96	4.12	3.05
Mean	76	68	59			5.82	5.32	4.26		

TABLE 2.—*The Mean Blood Pressure and Total Peripheral Resistance of Five Normotensive and Five Hypertensive Men before and during Four Hours of Sedation with Sodium Amytal*

Subject	Mean B.P., mm. Hg					Total Peripheral Resistance Dynes cm.$^{-5}$ sec.				
	Control	Hours after First Dose				Control	Hours after First Dose			
		1	2	3	4		1	2	3	4
Normotensive										
A	94	114	108	111	109	724	1474	1151	1286	1496
B	85	88	89	78	92	878	1347	1581	903	835
C	99	96	100	100	99	1072	1218	1464	1480	1482
D	75	85	82	86	89	806	976	687	1005	905
E	86	90	88	93	103	924	1332	1447	1277	1595
Mean	88	95	93	94	98	881	1269	1266	1190	1263
Hypertensive										
F	181	180	163	181	174	2153	2694	3446	2965	3330
G	149	142	140			1796	1542	1798		
H	106	117	115	126		2393	2291	3063	3290	
I	194	184	136			1941	2252	2568		
J	133	131	112	129	140	1808	2209	1797	2490	3656
Mean	153	151	133			2018	2198	2534		

Simultaneous records of blood pressure and cardiac output were made every hour until the experiment was terminated four hours after the first dose of Sodium Amytal. In three experiments it was necessary to discontinue the procedure earlier because the subjects became restless as the sedative action of the Sodium Amytal was diminished. The majority of subjects slept soundly during the last two and one-half or three hours of the procedure. All of the subjects were sedated to the sleep level at some time during the experiment. In most instances it was possible to deflate the mattress and connect the pressure recording system without disturbing the subject.

RESULTS

In both normotensive and hypertensive groups there was a marked decrease in cardiac output which was primarily the result of a decrease in stroke volume (table 1). The decrease was roughly 20 per cent in each of the groups. The mean blood pressure remained unchanged in the control group and decreased somewhat in the hypertensive group (table 2). In both groups the total peripheral resistance rose. The Fisher T test was used to test the differences between the mean of the control period and the mean of the different time intervals after administration of Amytal. This analysis showed that the changes in cardiac output and peripheral resistance in the control group at one, two and three hours after Amytal were significant at the 5 per cent level of probability. The hypertensive group showed a somewhat larger variability. The T test indicated that the difference between the mean cardiac output in the control period and that at the end of two hours sedation closely approached the 5 per cent level of probability. The T value was found to be 2.73 while T 0.05 = 2.77. Perusal of table 2 shows that at the end of the second hour, the mean blood pressure was lower and the peripheral resistance higher than the corresponding control values in 4 of the 5 hypertensive subjects.

DISCUSSION

The results obtained do not, therefore, support the view that Sodium Amytal causes a decrease in the blood pressure of hypertensive patients by lowering the total peripheral resistance. On the contrary, the drug appears to

cause a significant increase in total peripheral resistance and a decrease in cardiac output. If the latter is sufficiently marked, a decrease in mean blood pressure results *in spite of* the increase in total peripheral resistance. Little or no change in mean blood pressure is seen if the changes in the two opposing effects are more or less equal. The theoretic basis for the Amytal test as a means for selecting candidates for sympathectomy seems to be highly dubious, if not invalid.

The conditions of the experiments do not, of course, duplicate those of the Amytal test as ordinarily carried out. Some of the procedures, such as femoral puncture and inflation and deflation of the air mattress, were undoubtedly somewhat disturbing to the subject. It is not likely, however, that the disturbances played a significant role in determining the nature of the experimental results. For example, the difference in the cardiac output before and after the introduction of the Cournand needle into the femoral artery was only 300 cc. and was not statistically significant. It is also apparent that under the experimental conditions a definite decrease (up to 48 mm. Hg) in the mean blood pressure was observed in all but one of the hypertensive subjects. The Sodium Amytal test as performed in the experiments was, therefore, qualitatively if not quantitatively comparable to the test as ordinarily carried out.

In view of the changes in mean blood pressure in the hypertensive subjects, it is of interest to inquire into the validity of the factors used to convert the ballistocardiographic forces to cardiac outputs at different blood pressure levels. Nickerson and co-workers[3] have shown that over a wide range of blood pressures, cardiac outputs determined by the ballistocardiograph correlate well with cardiac outputs determined by the Fick principle (catheterization). In this laboratory comparisons were made between duplicate measurements of the cardiac output by the acetylene method corrected to direct Fick levels[4] and the ballistocardiograph in 18 hypertensive and 42 normotensive individuals whose ages were between 47 and 56 years. It was found that the relationship between the acetylene and the ballistocardiographic cardiac outputs did not change over a wide range of blood pressures.[9]

The pre-Amytal cardiac outputs in the control group were somewhat higher than the comparable figures for the hypertensive group. This difference is undoubtedly related to the decrease in the cardiac output that occurs with age, the evidence for which has been recently reviewed by Tanner.[5]

The effect of barbiturates on the cardiac output in animals has not been studied by the direct comparison of cardiac output measurements before and after administration of the drug in a manner similar to that employed in the Amytal test with man. However, in accord with the present results, there is ample evidence to demonstrate that continued barbiturate anesthesia depresses the cardiac output in dogs. For example, Shore, Holt, and Knoefel[6] found that the cardiac output of dogs decreased by as much as 50 per cent during the first four hours of sodium barbital anesthesia. In the same animal, Blalock[7] reported decreased cardiac output during the first 90 minutes under barbital anesthesia.

It is apparent, therefore, that barbiturates, and particularly Amytal, tend to depress the cardiac output. In the normal individual an increase in the total peripheral resistance maintains the blood pressure at normal levels. In the hypertensive patient a falling blood pressure during sedation with Amytal may merely represent the failure of the vasoconstricting mechanisms to keep pace with the decreasing cardiac output. A relative hypotension may be produced by Amytal as a result of excessive decline in cardiac output, or insufficient vasoconstriction, or both. In this small series the several possibilities are illustrated. An important decline in mean blood pressure may occur in the face of a substantial *rise* in the peripheral resistance. At the second hour patient 1 exhibited a fall of 58 mm. in mean blood pressure and a rise of 32 per cent in the peripheral resistance; this response is explained by a 47 per cent decline in cardiac output.

There is no evidence in any of the data presented that sedation with Sodium Amytal depresses the vasoconstrictor center or causes a relaxation of the peripheral arterioles. The

physiologic evidence, then, gives ample support to the view, as presented by de Takats, Julian and Fowler,[8] that the Amytal test does not identify patients who are suffering from neurogenic hypertension. As a test of the ability of the peripheral arterioles to relax, there is no support whatever for the Amytal test. Conceivably, the Amytal test might be used for the very different purpose of assaying the capacity of the vessels to undergo further marked vasoconstriction (patient F), or of the heart to withstand the depressing effect of Amytal (patient G). Neither of these factors appears to have much relevance to the selection of patients for sympathectomy.

Summary and Conclusions

1. Five normal young men were sedated with Sodium Amytal for four hours. Simultaneous mean intra-arterial blood pressures and cardiac outputs were determined by the ballistocardiographic method during a control period and at hourly intervals after administration of Amytal.

2. Similar observations were obtained on 5 male hypertensive individuals.

3. The characteristic response in both groups was a decrease in the cardiac output and an increase in the peripheral resistance. The mean blood pressure remained unchanged in the normal group and decreased somewhat in the hypertensive group.

4. No evidence was found to show that Amytal sedation causes a relaxation of the arterioles.

5. The mechanism for the fall in blood pressure observed in hypertensives during Amytal sedation was discussed.

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Cheyne-Stokes Respiration in Patients with Cardiac Enlargement and Prolonged Circulation Time

By WILLIAM W. PRYOR, M.D.

A study has been made of arterial blood changes during the respiratory cycle in patients with cardiac enlargement, prolonged circulation time, and Cheyne-Stokes breathing. In these patients, Cheyne-Stokes breathing appeared to depend upon the delay in passage of blood from the lungs to the arterial chemoreceptors and respiratory center. This delay allowed cyclic over- and underventilation. There was little or no central nervous system depression. In contrast, one case of Biot's breathing is presented as an example of another mechanism responsible for periodic breathing. Here irregular breathing seems to depend on fluctuations in activity of a severely damaged central nervous system.

CHEYNE-STOKES respiration is a rather common finding in cardiac failure, but the mechanisms involved in its production are poorly understood. This study is directed primarily toward investigating the role of cardiac enlargement with resulting circulatory delay as a factor in producing such cyclic respiration. One case of Biot's breathing is included as an example of an entirely different mechanism producing periodic respiration.

METHODS

Respiratory tracings were recorded by use of a Manning pneumograph. This consists of a section of corrugated rubber tubing stretched lightly across the chest and connecting with a tambour-type recording instrument. Arterial blood was obtained from the brachial artery through an in-lying arterial needle. The time required to obtain each sample varied between 5 and 12 seconds with an average of approximately 8 seconds. Carbon dioxide content was measured gasometrically[1] and pH was determined by use of an inclosed glass electrode. The carbon dioxide tension was calculated from these two values and from the hemoglobin. Per cent arterial oxygen saturation was measured by a spectrophotometric method.[2] The arm to tongue circulation time was measured with Decholin and the arm to lung time by ether. In some instances, Evans Blue dye was injected into an arm vein and samples of arterial blood taken to obtain vein to artery circulation time.

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RESULTS

Observations were made on 5 patients with Cheyne-Stokes breathing and cardiomegaly, and one patient with Biot's breathing. The data obtained from these patients is presented in the table. For each patient there are a number of arterial blood samples, taken at different phases of the respiratory cycle. The table indicates the duration of hyperpnea or apnea at the time each sample collection was finished. The values given for each sample are per cent blood oxygen saturation, whole blood carbon dioxide content, carbon dioxide tension, and pH.

The 5 patients with Cheyne-Stokes breathing and cardiomegaly show certain common features. First, ventilation responded in the usual way to the state of the arterial blood. That is, with low oxygen saturation and high carbon dioxide tension, there was hyperpnea, and, with the reverse situation, apnea. In the second place, there was a considerable lag between changes in ventilation and the resulting effects on the arterial blood. That is, hyperventilation was slow in raising the per cent oxygen saturation and reducing the carbon dioxide tension. Once these changes began, they continued far into the succeeding period of apnea. The arterial oxygen saturation was lowest and the carbon dioxide tension highest at the height of the hyperpneic phase; the oxygen saturation

was highest and the carbon dioxide tension lowest during the apneic phase. These patients all had prolongation of the circulation time and marked cardiac enlargement. In most of the patients, respiration was sensitive to chemical stimuli. This conclusion is based on the finding that breathing began at levels of arterial carbon dioxide tension which are below the normal resting range. Clinically, this group of cyclic breathers was distinguished not only by cardiac enlargement, but also by a relatively good sensorium, with little or no cyclic depression in apneic phases.

It would appear from the data that a marked increase in circulation time can set the stage for periodic breathing. Since blood from the

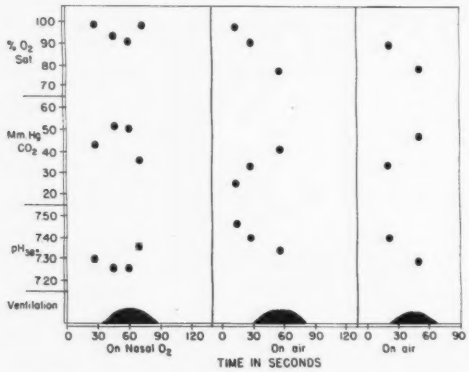

FIG. 1. Patient C. S., with hypertension, marked cardiomegaly, cardiac decompensation. Decholin circulation times 38 and 45 seconds; ether 13 seconds.

lungs is slow in reaching the chemoreceptors and respiratory center, overventilation, or apnea, can continue for a considerable time before altered blood can arrive at a sensitive region to correct the situation. Meanwhile, a large "backlog" of overaerated or underaerated blood has accumulated in the pulmonary veins and the dilated heart. While the respiratory center is responding appropriately to this blood, the blood passing through the lungs is being altered in the opposite direction. Once started, periodic breathing is self-perpetuating because of the delay in communicating events in the lungs to the respiratory center.

Periodic breathing, in this set of circumstances, can be started by a short period of overventilation. Maintained periodic breathing could be started in these patients by voluntary hyperventilation. This was particularly easy in C. S., who had a Decholin circulation time of about 40 seconds. The administration of 5 per cent carbon dioxide to the point of beginning hyperpnea would also initiate periodic breathing. Conversely, periodic breathing could be eliminated by encouraging this patient to breathe voluntarily at times when he would otherwise have been apneic. In general, extraneous respiratory stimuli during the apneic phase tend to break up this type of cyclic breathing. The cycle is smoother and more persistent when respiration is left primarily to chemical regulation. The act of performing an arterial puncture will often eliminate cyclic breathing. General discomfort, conversation, and muscular motion will have a similar effect. A quiet environment and sedation by a small dose of morphine will reduce such extraneous stimuli and will promote cyclic breathing.

The lag between changes in ventilation and resultant changes in the arterial blood, which is basic to this type of cyclic breathing, is illustrated in figure 1. This figure is constructed from the observations on patient C. S.

A contrast to this type of cyclic breathing is presented by the last patient in table 1, R. E., whose data are arranged in figure 2. This is an example of Biot's breathing. Here there was no regularity, but long periods of breathing interrupted by periods of apnea. This patient was in deep coma as a result of a cerebral hemorrhage and increased intracranial pressure. Extensive pneumonia was also present. The vein to artery circulation time was 15 seconds. Corresponding to the poor pulmonary function, the per cent oxygen saturation was 60 to 80 per cent; the carbon dioxide tensions, 45 to 55 mm.; and the pH levels low. Even during long periods of breathing, these levels were maintained. When breathing stopped, there was a progressive increase in blood gas stimulus until respiration started and then the previous state was restored. Here the blood chemical stimulus increased early in apnea and decreased during breathing, a situation opposite to that described above. It is concluded that the respiration is not

TABLE 1.—*Arterial Blood Gas Changes during Cyclic Breathing*

Patient	Comment	Respiratory Cycle		% Arterial Blood O_2 Saturation	Blood CO_2 Vol. %	Arterial pH (38°C.)	Arterial CO_2 Tension mm.Hg
		Duration of Apnea (Sec.)*	Duration of Hyperpnea (Sec.)*				
(S. Male 5	Hypertension; marked cardiomegaly; cardiac decompensation. Decholin circulation times 38 and 45 seconds, ether 13 seconds. Cheyne-Stokes breathing	15		97.3	32.8	7.47	25
		30		90.4	38.2	7.40	33
			30	77.6	42.6	7.34	41
		30	0	88.9	39.1	7.40	34
			25	78.2	43.7	7.29	47
		† 30		99.0	40.6	7.30	43
		†	20	93.6	44.3	7.26	51
		†	32	91.5	44.5	7.26	51
		†	40	98.6	38.2	7.36	36
E. J. Male 46	Hypertension; cardiomegaly; cardiac decompensation. Decholin circulation time 50 seconds; vein to artery 40 seconds. Cheyne-Stokes breathing	17		94.7	37.0	7.31	37
		30		97.3	34.1	7.38	29
			17	98.3	32.9	7.41	27
		0	50	99.3	33.3	7.39	28
		11		99.4	33.8	7.39	26
			6	98.0	35.8	7.35	33
		40	6	97.3	36.2	7.35	33
			18	95.7	36.7	7.35	34
		0	44	98.7	35.2	7.43	27
		9		100.0	34.0	7.44	26
			18	98.3	37.4	7.34	35
W. H. Male 71	Hypertension; cardiomegaly; cerebral vascular accident with right hemiplegia; mentally clear, but lethargic. Vein to artery circulation time 18 seconds. Cheyne-Stokes breathing		8	94.8	43.3	7.35	41
			20	92.6	44.6	7.34	43
		8		96.1	40.4	7.40	34
			19	93.8	44.0	7.33	43
		0	51	96.5	39.5	7.41	33
		6	0	96.4	41.2	7.42	34
			8	96.3	44.0	7.34	42
			20	92.7	45.3	7.34	44
		0	33	95.8	41.8	7.42	34
W. R. Male 45	Idiopathic myocardial hypertrophy; cardiac decompensation. Decholin circulation time 38 seconds. Cheyne-Stokes breathing		5	89.1	49.0	7.39	41
			22	86.3	47.8	7.38	40
			44	97.2	43.4	7.50	28
		0	53	99.9	40.9	7.49	27
		18		99.0	45.3	7.43	34
		5		99.3	44.9	7.45	33
		19	0	93.1	48.5	7.41	39
			26	83.2	49.3	7.39	41
		0	46	94.7	44.8	7.47	31
		24	0	98.8	44.0	7.48	30

Table concluded on following page

* "0" time indicates sample taken at the beginning of the appropriate cycle.

† Patient breathing oxygen through a nasal catheter.

Double line indicates cycles were not contiguous.

TABLE 1.—*Concluded*

Patient	Comment	Respiratory Cycle		% Arterial Blood O_2 Saturation	Blood CO_2 Vol. %	Arterial pH (38°C.)	Arterial CO_2 Tension mm. Hg
		Duration of Apnea (Sec.)*	Duration of Hyperpnea (Sec.)*				
H. O. Male 25	Marked cardiomegaly, cause undetermined; cardiac decompensation. Decholin circulation time 30 seconds, ether 16 seconds. Cheyne-Stokes breathing	33	0	97.3	35.7	7.42	29
			14	95.5	38.1	7.42	32
			37	94.8	39.7	7.39	36
			50	95.5	39.5	7.39	35
		0	69	96.4	36.1	7.44	29
		35		97.3	35.1	7.44	28
			12	94.3	39.2	7.39	35
			32	91.5	41.5	7.39	37
			60	95.5	37.5	7.43	31
		0	83	98.5	33.8	7.47	26
		32	0	92.8	40.4	7.37	38
R. E. Male 55	Cerebral hemorrhage, deep coma. Vein to artery circulation time 15 seconds, ether 5 seconds. CSF pressure 340 mm. H_2O. Biot's breathing	31		63.1	50.9	7.32	48
		39		54.0	51.2	7.29	51
		44	0	43.5	52.4	7.31	50
			11	39.4	52.6	7.29	53
			26	40.6	51.3	7.29	51
			60	61.8	47.4	7.31	46
			180	66.4	48.1	7.31	46
			290	69.8	47.7	7.33	44
			354	73.9	49.3	7.31	47
			416	72.2	50.3	7.31	48
		13		67.3	50.5	7.28	52
		21		59.9	51.2	7.27	54
		31		53.5	52.1	7.27	54
		0	265	73.6	50.1	—	—
		40	0	52.8	52.6	7.28	54

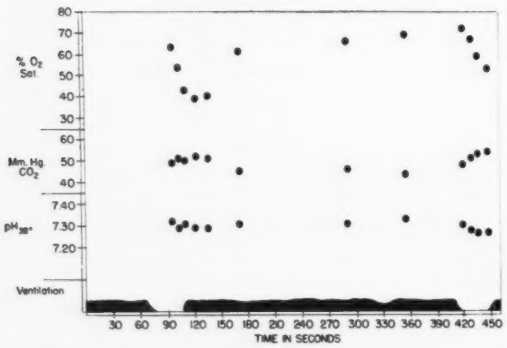

FIG. 2. Patient R. E., with cerebral thrombosis, and deep coma. Vein to artery circulation time 15 seconds; ether 5 seconds.

responding to changes in arterial blood, but that ventilation changes, and consequent blood gas changes, are secondary to fluctuations in activity of a severely damaged central nervous system. In this type of irregular breathing, Eyster found that the blood pressure rises during the period of apnea just prior to breathing and concluded that this restored circulation to the respiratory center made anoxic by increased intracranial pressure.[3] However, it would also seem possible to conclude that this rise in blood pressure is part of a general increase in excitability of the central nervous system and that the respiratory center itself shares in this increased activity.

DISCUSSION

Illustrations have been given of two different clinical situations in which periodic breathing is caused by entirely different mechanisms. The first is primarily dependent on circulatory delay between the lungs and respiratory center secondary to cardiac enlargement. In the

second, there seems to be fluctuation in activity of a severely damaged nervous system. In addition, periodic breathing of the classic Cheyne-Stokes type often occurs without a prolonged circulation time or cardiac enlargement. The mechanism responsible for this type of cyclic respiration has not been included in the present study.

Klein, from his study of Cheyne-Stokes respiration, also concluded that a prolonged circulation was important in producing periodic breathing.[4] Anthony and associates denied the importance of a prolonged circulation time.[5]

Nylin has shown that in cardiac enlargement there is a great increase in residual heart blood.[6] Material injected into a vein appears more slowly than normal in the arterial blood. Even more striking is the slow rate at which the arterial concentration builds up after the first appearance of the material. In cardiac failure a large volume of either under- or overaerated blood may be stored in the heart as residual blood. This leads to a prolonged ejection of blood which carries either too great or too little a stimulus to maintain normal respiration. Even though the measured Decholin or vein to artery circulation time may be only moderately prolonged, the presence of cardiac enlargement is an important factor.

A delay in acquainting the respiratory center with the effects of ventilation on the pulmonary blood appears to be fundamental in the causation of this type of periodic breathing. The basic delay is that of the circulation. In addition, at least two other variable lags may occur and thus influence the rate of cycling. These result from the buffering effect of the gas in the lungs during early apnea and from the time required for arterial blood changes to affect the respiratory center. In the lungs, following hyperpnea the alveolar oxygen partial pressure is high and the carbon dioxide partial pressure is low. This well washed residual air provides a reservoir for aerating blood coming to the lungs and prevents a rapid increase in the partial pressure of carbon dioxide and fall in the partial pressure of oxygen in the pulmonary venous blood during early apnea. This buffering action will have the effect of prolonging the apneic period.

In the patients with congestive heart failure and pulmonary edema, the buffering effect is somewhat reduced, and anoxia becomes a significant respiratory stimulus. It has been shown by Engel and co-workers that the factor of anoxia reduces the time of breathholding in normal subjects at high altitudes.[7] The added stimulus of a low arterial oxygen tension forces the resumption of respiration at a lower arterial carbon dioxide tension than at sea level. In pulmonary congestion because of a reduction in volume of air contained in the lungs,[8] the oxygen tension of alveolar air may fall more rapidly than usual during apnea. In addition any increase in alveolar-arterial oxygen gradient caused by edema will also reduce the arterial oxygen tension. In the cardiac patient, therefore, the arterial oxygen tension may fall rapidly enough during apnea to constitute a significant respiratory stimulus in addition to that caused by the rising carbon dioxide tension. If such a patient breathes a mixture containing a high oxygen partial pressure, the arterial oxygen partial pressure does not fall to a level which constitutes a significant respiratory stimulus, and arterial carbon dioxide partial pressure rises to a higher level before breathing begins. In the case of C. S. (fig. 1), cycling continued when the inspired air was enriched with oxygen. The arterial per cent oxygen saturation rose and remained high throughout the cycle. The arterial carbon dioxide tension fluctuated at a level appreciably higher than before.

The second delay is that between the arterial blood and the respiratory center. It must take some time for the carbon dioxide partial pressure of the center itself to change and with the rapid fluctuations occurring in the blood, the center lags behind. Such a lag has been described by Douglas and Haldane as the "flywheel" which normally prevents minor changes in alveolar and arterial carbon dioxide from disturbing breathing.[9] However, with the rapid and significant falls in carbon dioxide partial pressure which occur during hyperpnea, this stabilizing effect is lost and the lag of the carbon dioxide partial pressure of the center behind that of the arterial blood actually pro-

moted cyclic breathing. This delay may explain why breathing stops at a lower level of carbon dioxide tension than required to start respiration.

The group of patients in which cyclic breathing is based upon great prolongation of the circulation time comprises a small fraction of the total group of patients with cyclic breathing. Clinically, this group is distinguished by relatively little depression of the sensorium. Even in this group, however, the development of cyclic breathing is facilitated by central depression. Central depression is believed to operate in this group by reducing to a minimum all respiratory stimuli other than those due to blood chemical changes. This avoids accidental interruption of the cycle.

Summary

Observations have been made on arterial blood changes during the respiratory cycle in patients with cardiac enlargement, prolonged circulation time, and Cheyne-Stokes breathing. In these patients, Cheyne-Stokes breathing appeared to depend upon the delay in passage of blood from the lungs to the arterial chemoreceptors and respiratory center. This delay allowed cyclic over- and underventilation.

Acknowledgment

The author wishes to express appreciation for the advice and assistance of Dr. John B. Hickam and Miss K. Regina Frayser.

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Selective Synchronous Recording of the Ballistocardiogram and Electrocardiogram on a Single Channel

By RICHARD GUBNER, M.D.

Identification of ballistocardiographic waves is difficult unless reference can be made to another simultaneously recorded event in the cardiac cycle. By hooking up an electrocardiographic lead in parallel circuit with the ballistocardiograph and interposing a rheostat of variable resistance in series in one of the electrocardiographic lead wires, the electrocardiogram may be selectively tuned in or out of the circuit. At resistances of 50,000 to 100,000 ohms the QRS complex appears only as a small spike preceding the ballistocardiographic waves and readily permits their identification. This simple expedient renders unnecessary the use of multiple recording channels in clinical ballistocardiography.

THE introduction of simplified technics for recording ballistocardiograms[1] has placed ballistocardiography within reach of all who possess an electrocardiograph, which may be used to inscribe ballistocardiograms made by electromagnetic, photoelectric or piezoelectric methods. A deterrent to general clinical employment of the ballistocardiograph, however, has been the necessity of employing a multichannel recording instrument for proper recognition of the ballistocardiographic waves by orientation to known phases of the cardiac cycle, such as the electrocardiogram and heart sounds. When ballistocardiographic patterns are abnormal it is difficult or impossible to identify the individual waves properly, unless simultaneous registration is made of another event in the cardiac cycle.

Simultaneous recording of two different wave forms (that is, heart sounds and electrocardiogram) with a single beam tube has been accomplished by use of two valve amplifiers and an automatic high frequency electronic switch which connects their output alternately to the single deflecting plate of the tube.[2]

A simple expedient which permits simultaneous recording of the ballistocardiogram and the electrocardiogram with freely selective amplitudes of either wave form is illustrated in figures 1 and 2. An electrocardiographic lead is hooked up in parallel circuit with the ballistocardiographic terminals, with a rheostat (variable resistance zero to 1,000,000 ohms)* interposed in series in one of the electrocardiographic lead wires (fig. 1).

With low resistances the electrocardiogram dominates, but as the resistance is stepped up the amplitude of the electrocardiographic waves decreases to a point where the QRS appears only as a small spike preceding the ballistocardiographic waves with each heart beat. This serves as a convenient reference for timing and identifying the waves of the ballistocardiogram. The appearance of the record with varying resistances is shown in figure 2. When resistance is increased to 200,000 ohms or above, the electrocardiogram becomes imperceptible and undamped ballistocardiographic waves are recorded. During recording of the ballistocardiogram the dial on the rheostat can be rapidly switched so that the electrocardiographic timing reference can be employed conveniently as desired (lower strip, fig. 2).

Simultaneous recording of the ballistocardiogram and electrocardiogram can be achieved by connecting both circuits in series,[3] but the procedure described offers the advantage of permitting selective damping of the electrocardiogram to a point where it does not disturb the configuration of the ballistocardiographic waves yet permits their identification.

From the Medical Department of the Equitable Life Assurance Society of the United States, New York, N. Y.

* A radio volume control unit serves conveniently.

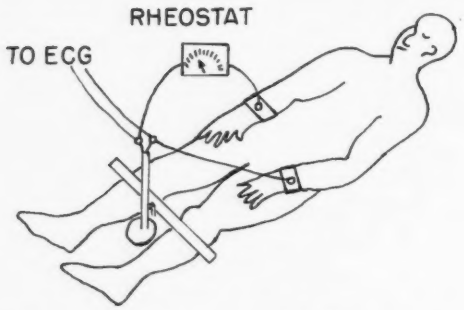

FIG. 1. Device for recording ballistocardiogram and electrocardiogram selectively on a single channel. Two electrocardiographic lead wires are hooked up with the ballistocardiograph terminals in parallel circuit, with a rheostat interposed in series in one of the electrocardiogram lead wires. Rheostat resistance is variable by dial from 0 to 1,000,000 ohms.

apart from facilitating identification of the waves. In normal subjects the peak of the J wave is attained within 0.25 second from the onset of the QRS complex, whereas in heart disease this interval may be increased to 0.30 second or more,[4] reflecting a lag both in the velocity of left ventricular ejection and acceleration of the blood column in the aorta. In addition to prolongation of the QRS-J peak interval, other abnormalities associated with impaired force of cardiac contraction include slurring, notching and lowered amplitude of the J wave, disappearance of the I wave, and increased prominence of the H wave. Such abnormalities assume greater significance when they are present with respiration suspended, for, as indicated elsewhere,[4, 5] respiratory variation of the

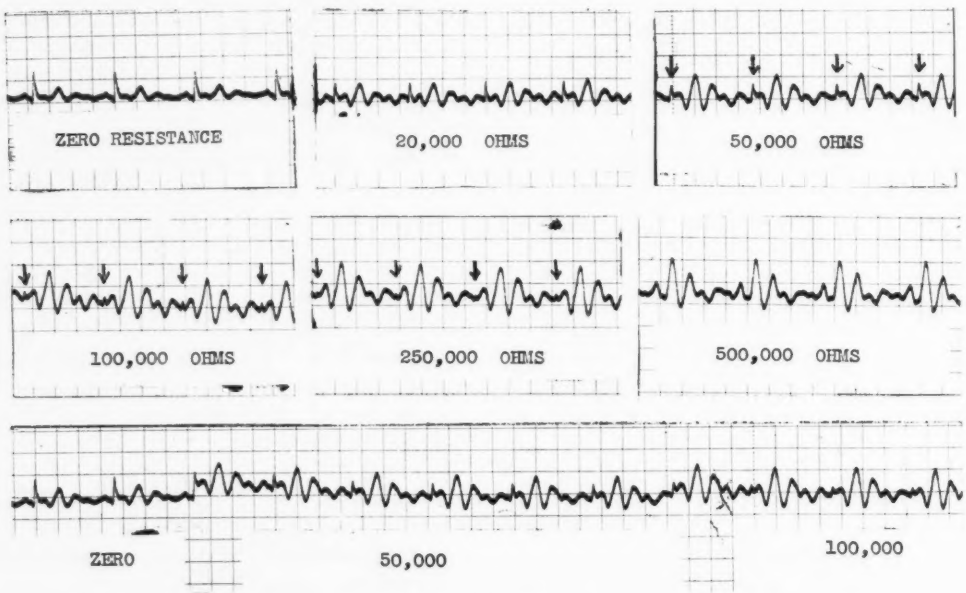

FIG. 2. Simultaneous recording of electrocardiogram and ballistocardiogram on single channel. At low resistance the electrocardiogram dominates. As the resistance is increased to 50,000 ohms and above, the amplitude of the QRS is markedly diminished so that the QRS complex is visible only as a small spike preceding the ballistocardiographic waves with each beat. This serves conveniently for timing and identification of the ballistocardiographic waves. In the lower strip the resistance is abruptly increased during continuous recording, first to 50,000 ohms and then to 100,000 ohms. Note marked decrease in amplitude of the QRS complex and emergence of the ballistocardiographic waves as resistance is increased.

Synchronous recording of the electrocardiogram with the ballistocardiogram is of value

ballistocardiographic waves is determined in important measure by extracardiac influences

associated with phasic respiratory changes in peripheral resistance and aortic capacity.

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Coarctation of the Aorta Complicated by Patency of the Ductus Arteriosus

Physiologic Considerations in the Classification of Coarctation of the Aorta

By Arnold L. Johnson, M.D., Charlotte Ferencz, M.D., F. W. Wiglesworth, M.D., and Donald L. McRae, M.D.

The study of the anatomic and hemodynamic relationships in a case of coarctation of the aorta complicated by patency of the ductus arteriosus and pulmonary hypertension indicated the necessity for a physiologic approach to the classification of coarctation of the aorta. The origin of existing classifications has been briefly traced and basic anatomic and physiologic considerations in this malformation have been reviewed. A classification is presented which takes into account the state of the ductus arteriosus, its relationship to the coarcted segment and the influence of the collateral circulation. The microscopic appearance of the pulmonary vessels is included.

THE exact diagnosis of coarctation of the aorta is now a matter of great practical importance. No particular diagnostic problem is involved in the usual "adult" type of coarctation. There are, however, cases which are complicated by the presence of a patent ductus arteriosus. Such a complication may present diagnostic difficulties of which the case presented below is illustrative. The purpose of this paper is to discuss certain hemodynamic relationships in these cases, the means involved in diagnosis and to suggest a scheme of classification arising out of these considerations.

The classification of coarctation of the aorta has always presented considerable difficulty. The emphasis has been placed upon anatomic and embryologic considerations. It is apparent, however, that physiologic adjustments, dependent upon various arrangements of the ductus arteriosus and collateral circulation, modify the effect of the area of stenosis. Thus a classification based not only upon anatomic, but also upon hemodynamic considerations may be useful in the study of this group of malformations.

Coarctation of the aorta occurs in the region of the junction of the fourth and sixth embryonic arches, represented by the arch of the aorta and by the ductus arteriosus, respectively. Above the ductus arteriosus, lying between it and the left subclavian artery, is an important segment of the aorta through which, in fetal life, very little blood flows. Left ventricular blood is directed to the head and upper extremities above this segment, and right ventricular blood flows to the trunk and lower extremities through the ductus below it. This portion of the aorta, known as the isthmus, becomes functional when the ductus closes and it then serves to connect the cephalic and caudal arterial circulations. During fetal life the isthmus is narrow and dilates gradually after the blood flow through it is established.

These basic facts were considered by early writers attempting to clarify the pathogenesis of coarctation of the aorta. Bonnet,[1] Hamilton and Abbott[2] and Blackford[3] have reviewed the various theories and it appears that these followed along three main lines of thought. Many workers favored the view that the condition was due to persistence of excessive narrowing of the isthmus and some thought that this process might be influenced by traction of the obliterating ductus. Others believed that the abnor-

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Aided by a Grant from the National Research Council of Canada. One of us (C. F.) was Molson-McConnell Research Fellow in Medicine, 1948-1949.

Read by title, The American Surgical Society, April 1950, Colorado Springs, Col.

mality occurred during the process of joining of the embryonic arches. The third group suggested that closure of the ductus arteriosus was responsible for the development of the condition. It was believed that a thrombus might extend from the aortic orifice of the ductus into the aorta, or that the "peculiar" tissue might either be present in the aortic wall or extend to it from the ductus and by its contraction promote an area of stenosis in the aorta.

Considering these various theories, Bonnet concluded that the existent controversy resulted from the failure to recognize two main classes of coarctation: (1) the "infantile" type, representing a persistence of the fetal condition of the isthmus, and (2) the "adult" type, being related to closure of the ductus arteriosus.

This classification clarified the study of coarctation considerably and was widely adopted. It became apparent, however, that many cases could not be allocated satisfactorily to the categories provided, and further classifications[4, 5] based on anatomic considerations, have been presented. Little emphasis has been placed upon important adaptive changes which significantly alter the hemodynamic relationships. Taussig[6] pointed out the importance of the ductus arteriosus in affecting the nature of the anomaly. If, in addition, the collateral circulation is considered, it appears that a useful differentiation of types would depend upon the state of the ductus, its entry into the aorta relative to the site of coarctation, and upon the state of the collateral circulation.

This view was suggested by the correlation of hemodynamic and necropsy findings in a case of coarctation of the aorta associated with a patent ductus arteriosus. This case possessed the characteristics of both Bonnet's "adult" and "infantile" types anatomically, but physiologically was almost entirely of the "adult" variety. The findings which initiated our interest in this problem are presented below.

Case Report

The presenting complaint of this 9½ year old white girl was a considerable limitation of activity due to dyspnea ever since she learned to walk. There was no cyanosis or clubbing. There was no difference between the color of the fingernail and toenail beds. There was a harsh systolic murmur of moderate (grade III) intensity maximal in the fourth left intercostal space, transmitted particularly well to the left axilla and back. The murmur was not prominent over the spine. In addition there was a continuous murmur, of slight intensity, heard over a fairly localized area in the second intercostal space close to the left sternal border. The blood pressure in the arms was 168/84. The femoral artery pulsations could just be felt and the blood pressure in the legs was 96/78. Pulsations of the intercostal vessels could be felt easily in the seventh to the last intercostal space bilaterally, but no pulsations were felt beneath the medial border of either scapula. The clinical diagnosis was coarctation of the aorta associated with a patent ductus arteriosus.

On fluoroscopic examination the heart appeared to be considerably enlarged in both the posteroanterior and oblique projections. The pulmonary artery and its branches were thought to be normal in size or slightly enlarged. The left ventricle was definitely enlarged. There was questionable evidence of notching of the fourth and fifth ribs bilaterally.

The electrocardiogram showed a right axis deviation in the standard leads. The unipolar precordial leads showed a pattern which was thought to be compatible with right ventricular hypertrophy.

A finding of considerable interest was the difference noted between the percentage oxygen saturation of the femoral artery blood and that in the upper part of the body. On two occasions the saturation of blood withdrawn from the femoral artery was found to be 91.6 per cent and 92.7 per cent. Employing the oximeter[7] on the ear, three readings were each 98 per cent. It was felt that this represented a significant difference between the oxygen saturation of blood flowing to the upper extremities and that flowing to the lower extremities.

Heart catheterization[8] studies revealed that the pressures in the right ventricle and in the pulmonary artery were greatly increased: right ventricle 90/16 and pulmonary artery 92/72. The oxygen content of blood samples in the right auricle and right ventricle was similar and thus there was no evidence of either an auricular or a ventricular septal defect (table 1). The oxygen content of blood from the main pulmonary artery was 0.7 volumes per cent greater than any sample from the right ventricle.

At one site, distal to the main pulmonary artery, the oxygen content was considerably higher and showed a value of 18.3 volumes per cent, similar to that obtained in the femoral artery. The position of the catheter tip could not be ascertained definitely. It was felt that it could be in a branch of the pulmonary artery or possibly have passed through a ductus into the descending aorta. The latter anatomic arrangement had been suggested by the finding of slight oxygen unsaturation of the femoral

artery blood. On the other hand, it was argued that if the ductus communicated with the descending aorta, then the unsaturation would have been much greater and there should have been cyanosis of the toenail beds.

It will be apparent shortly that insufficient attention was paid to the similarity of the pressure readings in the pulmonary artery and the femoral artery. The intrafemoral arterial pressure was 102/80, and the pressure in the pulmonary artery was 92/70. Unfortunately these were not simultaneous recordings.

The angiocardiograms showed the dye filling the right auricle and ventricle and passing into the lungs through a considerably enlarged pulmonary artery. There was no evidence of over-riding of the aorta. The cavity of the left ventricle appeared to be enlarged and its wall thickened. The curvature of the ventricular septum appeared to be convex toward the right ventricle. Dye was seen in the axillary arteries but none in the descending aorta or in the left gastric or renal arteries.

TABLE 1.—*Data from Heart Catheterization*

	Oxygen (vols. %)	Pressure (mm.Hg)
Femoral artery	18.3	102/80*
Capacity	19.9	
% Saturation	92.7	
Superior vena cava	14.2	
Upper right auricle	14.1	
Mid right auricle at tricuspid valve	14.0	
Lower right ventricle	14.5	
Mid right ventricle	14.7	
Upper right ventricle	13.9	90/16
Main pulmonary artery	15.4	92/74
Query position (see text)	18.3	84/64

* The pressure was recorded the day following the cardiac catheterization.

It had been quite evident on clinical grounds that this patient had a coarctation of the aorta with a well developed collateral circulation. It was also thought that a patent ductus arteriosus was present. The subsequent investigation then revealed findings which were not readily explained. The electrocardiogram was not in keeping with the left ventricular enlargement expected in coarctation and demonstrated in the angiocardiogram. It was, however, compatible with the right ventricular hypertrophy considered to be present after the high right ventricular and pulmonary artery pressures had been recorded during heart catheterization. This increased pressure was a surprising finding. Was it due to a primary lung condition or secondary in some way to the presence of the ductus?

At operation the site of the coarctation appeared to be quite localized and distal to the aortic end of the ductus. The left pulmonary artery and the very short ductus were obviously dilated. During the dissection, which was a matter of considerable difficulty, uncontrollable hemorrhage occurred from a tear in the left pulmonary artery.

Autopsy Findings

At postmortem examination the abnormal findings were confined to the cardiovascular system. The heart was moderately to markedly enlarged and weighed 300 Gm. as compared with the normal average weight of 155 Gm. The cardiac enlargement was due almost entirely to increase in the ventricular mass. The chamber of the right ventricle was not dilated, but that of the left ventricle showed moderate dilatation. The thickness of the right ventricular wall varied from 0.4 cm. to 1.0 cm. (normal 0.15 to 0.3 cm.). The thickness of the left ventricular myocardium varied between 0.4 cm. and 1.4 cm. (normal 0.3 to 1.1 cm.). It would thus appear that the right ventricle showed a relatively greater myocardial hypertrophy than the left.

FIG. 1. Anterior view of great vessels. The large pulmonary artery is laid open. Ascending aorta normal. Arteries arising from the arch increased in circumference. The ductus (held open by the hooks) is continuous with the descending aorta. The proximal opening of the coarcted segment into the superior surface of the ductus is well shown.

The pulmonary and tricuspid valves were normal, the aortic valve was bicuspid, but otherwise was not remarkable, and the mitral valve showed a rare anomaly, a double orifice.

On external examination of the great vessels (fig. 1) the main pulmonary artery was much larger than the aorta, being of aneurysmal proportions.

The right and left pulmonary arteries were also enlarged. The circumference of the pulmonary artery was 6.5 cm. (normal 4.0 cm.) while the circumference of the ascending aorta was 4.2 cm. The proximal aorta was of normal circumference almost to the point of coarctation. It is interesting to note, however, that the innominate artery, the left common carotid, and the left subclavian arteries showed an increased circumference, averaging at least 0.5 cm. greater than controls. The descending aorta measured 2.5 cm. in circumference (control 3.0 cm.). The mouths of the intercostal arteries did not appear to be dilated. The circumference of the internal mammary arteries (0.9 cm.) equalled that of the common iliac arteries. There was thus evidence that the mammary arteries were dilated.

A short, broad patent ductus arteriosus arose from the beginning of the left pulmonary artery and was continuous with the descending aorta (fig. 1). In the fixed state it measured 0.4 cm. in length, and 2.0 cm. in circumference. The orifice of the coarcted segment of the aorta entered the ductus at its distal margin as it became continuous with the descending aorta. The stenosed orifice measured 0.1 cm. by 0.15 cm. in diameter. On the opposite wall of the ductus arteriosus was a slightly raised, yellowish, firm, rough lesion measuring 0.4 cm. in length by 0.5 cm. in width. Grossly and microscopically this was a "jet" lesion,[9] apparently the result of the blood flow coming from the coarcted aorta.

A second jet lesion was present on the left side of the ridge separating the right and left pulmonary arteries. This measured 0.5 by 0.2 cm. As this lesion lay only on the left side, it was presumably created by a flow of blood from the ductus into the left pulmonary artery.

The arch of the aorta between the left common carotid and the left subclavian arteries was normal in circumference, but narrowed rapidly immediately distal to the origin of the left subclavian artery. The isthmus of the aorta measured approximately 0.4 cm. in length, and funnelled to the point of actual coarctation. The isthmus terminated by turning sharply inferiorly and fusing with the superior surface of the ductus. At the actual site of coarctation no diaphragm could be seen such as described by Edwards and co-workers.[9] The opening was a simple stenosis caused by a uniform narrowing of the wall of the aorta (so-called infantile coarctation).

Microscopic examination of the lung tissue showed vascular lesions of moderate extent. Perhaps about one-third of the pulmonary vessels showed changes and they were more numerous centrally than peripherally. The large arteries showed no atherosclerosis and only occasional plaques of intimal fibrosis similar to that to be described.

The principal arteries involved were the medium and small type, varying from about 200 to 600 microns in diameter. The lesions were essentially intimal in situation and consisted of a concentric (occasionally excentric) fibroplastic proliferation of the intima (fig. 2). The collagenous tissue either contained numerous nuclei or was relatively acellular. The lumens showed varying reduction in size up to complete obliteration. Reduplication of the internal elastic lamina was not a prominent feature and was mostly focal. The adventitia was widened by dense connective tissue.

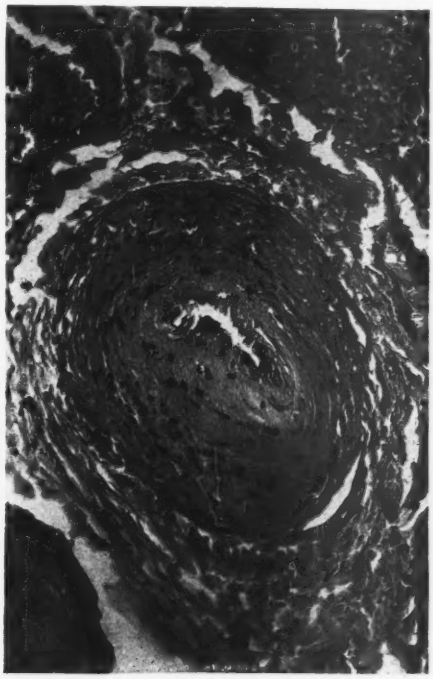

FIG. 2. Small pulmonary artery (about 200 μ) showing marked intimal fibrosis (inner four-fifths of wall thickness) and moderate atrophy of the media. The internal elastic lamina can be seen as a faint wavy line at top and right side. This vessel arose from a large artery and at its origin, 100 μ proxmally, was histologically normal. H. & E. × 160.

A striking feature was the definite elastosis of both large and small arteries. The elastic fibers were thick and in stained sections under low power magnification these vessel walls appeared almost solidly black. As a result, even in those arteries showing no intimal thickening, the whole wall was thicker and heavier than normal (figs. 3*A*, *B*). It is difficult to state whether there was actual increase in the number of elastic fibers but undoubtedly they were hypertrophied. They showed slight fraying and beading. Collagen stains revealed no increase in fibrous tissue in the walls of these elastic vessels.

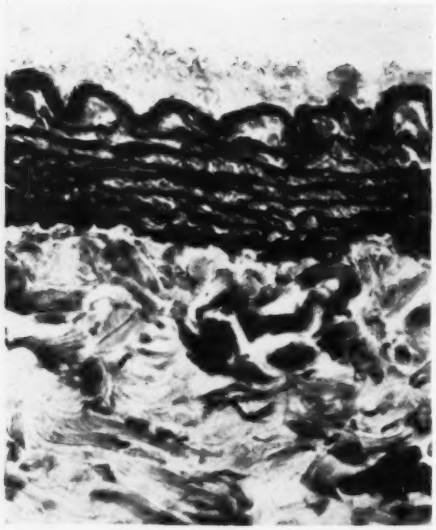

FIG. 3A. Pulmonary artery (about 900 μ) from a normal 11 year old child. For comparison with 3B. Weigert's elastic tissue stain. × 380.

FIG. 3B. Pulmonary artery (about 900 μ) showing wide and heavily elastified wall. There is no fibrosis. Weigert's elastic tissue stain. × 380.

There was no definite muscular hypertrophy in the media. A few vessels showed focal swelling and disappearance of the internal elastic lamina and occasionally there was focal fibrosis of the media with complete disappearance of the muscle. The arterioles, except for an occasional one, showed no lesion. The intimal changes of the small and medium sized arteries and the definite elastosis of all arteries are changes associated with stress, presumably hypertension. The absence of arteriolar lesions, and the fact that the intimal hyperplasia was not generalized in the presence of generalized vascular elastosis suggests that these lesions were the result, not the cause of the pulmonary hypertension.

DISCUSSION

The interest of this case centers about the anatomic and hemodynamic relations between the patent ductus and the coarctation of the aorta. Here we have virtual separation of the upper and lower aortic segments at the isthmus with marked development of a collateral circulation, features of the "adult" type; and a patent ductus which is continuous with the descending aorta, a characteristic of the "infantile" type.

Taussig[6] has made the important observation that where the descending aorta is fed mainly from the pulmonary artery, there may be cyanosis of the lower part of the body. From the evidence of our case it is apparent that it is also possible to have this free anatomic communication without cyanosis. The explanation for this lies in the pressure relationship which exists between the pulmonary artery and the descending aorta. In our case the pressure in the pulmonary artery was 92/74, and the intra-arterial pressure in the femoral artery (on the following day) was 102/80. It is evident that an efficient collateral circulation can maintain a considerable pressure in the aorta distal to the coarctation, and this pressure may be equal to or greater than that in the pulmonary artery.

The presence of a jet lesion in the ductus opposite the stenotic opening suggests that blood entered the ductus from the upper aortic segment. The finding of another jet lesion on the left side of the bifurcation of the main pulmonary artery may indicate that there was also a flow of blood from the descending aorta

into the pulmonary artery. This explanation of the manner in which the blood flows through the ductus gains support by the demonstration of blood in the pulmonary artery with an oxygen content higher than that noted in the blood from the right ventricle. Furthermore, the slight but definite unsaturation of the femoral artery blood indicates the entry of venous blood into the descending aorta. This may occur due to the formation of eddy currents or by a change in pressure relationships. It seems probable that the main flow through the ductus was from aorta to pulmonary artery.

The high pulmonary artery pressure, the dilatation of this vessel and its main branches, and the marked right ventricular hypertrophy, have added to the difficulty of explaining the hemodynamic relationships in this case. Edwards and co-workers,[10] in discussing the question of a systemic right ventricle supplying both the lungs and descending aorta, raise the point that one would expect the pulmonary vessels to exert a resistance similar to or greater than that in the systemic vessels. In this connection they have described changes in the small pulmonary arteries similar, in part, to those noted in our case. In addition, however, they observed arteriolar changes, which are not present in the case described. An adequate explanation for the pulmonary hypertension is not apparent.

The complicated features in the case presented led to a search for cases of coarctation in which the ductus was patent. In table 2 are listed 28 autopsied cases, over 1 year of age, which are arranged with regard to the site of the ductus and the state of the collateral circulation. The original references were not readily available for some of the earlier cases, and the data were obtained from manuscript notes in the Maude Abbott collection[11] and from Barié's article.[12]

The ductus was distal to the site of coarctation in 16 instances, and proximal in 5. In 4 cases the coarctation was described as occurring "at" the level of the patent ductus and in one "to the right" of it. In 2 cases the relationship was not described or was not apparent from the record. Among the 16 cases in which the ductus entered the aorta distal to the site of stenosis and communicated with the descending aorta, as in our case, there were 5 instances (table 2, cases 4, 5, 8, 16, 23), in which a collateral circulation was described. In none of these was there any mention of cyanosis in the lower extremities, and this suggests that the circulatory arrangement in these cases may have been similar to that in our case. The collateral circulation was not developed in the 2 cases (cases 27, 28, table 2) studied by Edwards.[10] Bramwell[5] mentions the absence of clinical evidence of a collateral circulation in his patient, but does not record the autopsy findings regarding this point. In 7 instances the collateral circulation is not mentioned and in one the ductus arteriosus was small, being almost obliterated by vegetations, and considered to be nonfunctional. The collateral circulation was well developed in all 5 cases in which the patent ductus lay proximal to the site of coarctation. Edwards points out that, if the stenosis is marked, this arrangement would be incompatible with fetal life unless collateral pathways developed early to ensure the return flow of blood to the placenta. However, this is not the sole mechanism by which collateral circulation develops because collateral circulation also occurs in cases where the ductus lies distal to the site of stenosis. In this latter group the fetal circulation is essentially undisturbed.

In the 16 cases (table 2) in which the pulmonary artery is continuous with the descending aorta through a ductus distal to the coarcted segment, there is no mention of cyanosis of the feet, and in 11 of these there is no mention of collateral circulation. If there is inadequate collateral circulation, the supply to the lower extremities would be mainly from the right ventricle and one would expect cyanosis in them. If collateral circulation is present, it does not rule out the possibility of cyanotic lower extremities, but renders it less likely. It appears quite possible that such a circulation may have been present in the above cases and yet not recognizable on physical examination or postmortem study.

Considerations arising out of the study of our present case and those cases noted above, em-

TABLE 2.—*Cases of Coarctation of the Aorta Associated with Patent Ductus Arteriosus*

No.	Reference	Date	Sex	Age	Rel. of C. to D.A.	Collaterals	Remarks
				Maude E. Abbott's Series[13]			
1.	Nixon[11, 12]	1834	M	27	"at"	Not mentioned	
2.	Chevers[14]	1845	M	"young"	above	Not mentioned	
3.	Babington[15]	1847	F	24	above	Not mentioned	
4.	Hamernjk[11, 12]	1848	M	17	above	Diagnosed clinically	
5.	Viaud-Grand-marais[11, 12]	1857	M	62	above	Dilated (int. mammary)	Two areas of stenosis
6.	Almagro[11]	1862	F	19	"at" (prob. above)		Aorta dilated below ductus
7.	Peacock[16]	1862	M	30	above	Not mentioned	Isthmus stenosis
8.	Redenbacher[11, 12]	1873	M	7	above	Extensive	Isthmus stenosis
9.	Fawcett[17] Case 3	1905	F	45	below	L. subcl. & carotid dilated	Gradual sten. below l. subcl.
10.	Case 11	1905	F	17	?	Dilated	D.A. admits bristle
11.	Case 15	1905	M	21	"to right"	Not mentioned	D.A. wider than a goose quill
12.	Horder[11]	1907	M	12	"at"	Not mentioned	
13.	Stauung[11]	1913	F	28	"at"	Not mentioned	
14.	Meixner[11]	1922	M	20	below	Dilated	D.A. finely patent
				Reifenstein, Levine and Gross' series[18]			
15.	deVries[19]	1918	M	3	above	Not mentioned	D.A. admits fine sound
16.	Ulrich[20]	1931	M	23	above	Dilated	
17.	Brotchner[21]	1939	M	33	below	Dilated	D.A. tiny cap. lumen only
18.	Blackford[3] Case 10	1928	F	23	above	Not mentioned	D.A. admits probe
19.	Evans[4] Case 2		M	30	above	Not described	
20.	Case 5		M	8	above	Not described	
21.	Kellogg & Biskind[22]	1934	M	16	above	Dilated	D.A. funct. closed
22.	Tillich[22]	1941	M	17	?	Not mentioned	
23.	Fagin, Shepeard & Morrison[23]	1946	M	18	above	Dilated	I.V.S.D.
24.	Bramwell[5]	1947	F	23	above	No rib notching. P.M. findings not mentioned	
25.	Edwards[10] Case 1	1949	F	15	below	Dilated	Pulm. vascular lesions
26.	Case 2	1949	M	22	below	Dilated	Pulm. vascular lesions
27.	Case 3	1949	F	23 mos.	above	None	Pulm. vascular lesions
28.	Case 4	1949	F	7	above	None	Pulm. vascular lesions

phasize the desirability of a more physiologic approach to the study and classification of coarctation of the aorta. If the ductus is proximal, Edwards, as noted above, observes that collateral circulation must develop in the embryo for life to be maintained. Thus, it is not pos-

sible to have a patent ductus proximal to the stenosis in the absence of a collateral circulation. If the opening of the patent ductus lies distal to the coarcted segment two circulatory arrangements are possible. The pressure maintained in the aorta distal to the coarctation by the collateral circulation may be low and blood from the right ventricle may enter the descending aorta by way of the patent ductus. On the other hand, the pressure maintained in the descending aorta may be adequate to prevent blood entering from the ductus and may cause a flow of blood from aorta to pulmonary artery. Where the pressures in pulmonary artery and descending aorta are similar it is quite possible to visualize eddy currents which might permit a mixing of blood in the two vessels. It is evident, therefore, that when there is a patent ductus distal to the coarcted segment, the degree of saturation in the femoral arterial blood will be dependent upon these pressure relationships.

This discussion may be summarized by presenting these variations in the form of a classification of coarctation of the aorta. It is assumed that the degree of stenosis is such that there is marked interference in blood flow into the descending aorta distal to the coarcted segment. The arrangement noted below is based upon anatomic and hemodynamic considerations arising out of the state of the ductus, the relationship of the ductus to the site of coarctation, and the adequacy of the collateral circulation. It is observed that while it is possible, on clinical or pathologic evidence, to state that collateral circulation is present, the absence of a collateral circulation may not be demonstrable by clinical or pathologic means.

Coarctation of Aorta

I. *Ductus Arteriosus Closed*
   (1) With collateral circulation
   (2) Without (or with inadequate) collateral circulation* (incompatible with life)

II. *Ductus Arteriosus Open*
   A. Proximal to coarctation
      (1) With collateral circulation
      (2) Without (or with inadequate) collateral circulation* (incompatible with life)
   B. Distal to coarctation
      (1) With collateral circulation
         (a) Pressure maintained by collateral circulation *adequate* to prevent flow from pulmonary artery to aorta.
         (b) Pressure maintained by collateral circulation *inadequate* to prevent flow from pulmonary artery to aorta.
      (2) Without collateral circulation*

* While the absence of a collateral circulation may not be demonstrated by clinical or pathologic means, it is at least a hypothetic possibility.

Such a scheme may be of help in assigning a case of coarctation to its proper category. If there is no suspicion of a patent ductus arteriosus, then the case falls into group I(1), which corresponds to the "adult" type. A complicated case may manifest itself by the associated signs of a ductus or by the demonstration of right ventricular hypertrophy or by cyanosis of the lower extremities. The decision as to whether the ductus lies proximal or distal to the site of stenosis may be clarified by determining the oxygen saturation of the femoral artery blood. If the ductus is proximal to the coarctation blood from the femoral artery is fully saturated. If cyanosis of the lower extremities is present the ductus is distal to the site of coarctation, and the collateral circulation is inadequate to prevent a venous-arterial shunt. If, in the femoral arterial blood, there is some unsaturation but insufficient to cause cyanosis, the ductus is also distal to the coarcted segment but the pressure, maintained by the collateral circulation in the descending aorta, approaches or may be higher than that in the pulmonary artery. It appears reasonable to suppose that when the pressure in the descending aorta is higher, femoral artery blood might be fully saturated or there might be some unsaturation due to eddy currents permitting blood from the pulmonary artery to enter the aorta.

Summary

A hemodynamic and pathologic study is presented of a case of coarctation of the aorta, complicated by a patent ductus entering the aorta distal to the coarcted segment. The interest of the case centers about the pressure relations of the pulmonary artery and the aorta. Pulmonary hypertension was present and there were microscopic pulmonary vascular lesions

which are described. The correlation of findings illustrates the importance of a more physiologic approach to the classification of coarctation of the aorta. Such a scheme is suggested, based upon the state of the ductus arteriosus, its relationship to the area of stenosis and the influence of the collateral circulation.

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The Diagnosis of Aortic Septal Defect by Retrograde Aortography

Report of a Case

By Benjamin M. Gasul, M.D., Egbert H. Fell, M.D. and Raul Casas, M.D.

This rare congenital malformation is a round or oval opening between the ascending aorta and the main pulmonary artery above the semilunar valves. It is practically impossible to differentiate this malformation from a patent ductus arteriosus clinically because both malformations may present the same physical, fluoroscopic, roentgen and electrocardiographic findings. Even angiocardiography and cardiac catheterization do not differentiate these congenital malformations. The authors have studied 2 patients with aortic septal defects. One was operated at another clinic for a suspected patent ductus arteriosus, and the other case presented here was diagnosed by retrograde aortography.

THE DIAGNOSIS of congenital aortic septal defect is one of the most difficult in the field of congenital malformations of the heart. Fortunately, it is one of the rarer malformations. A thorough review of the literature has revealed 24 reported cases.

During the past four years, we have encountered 2 cases of aortic septal defect. One, a 9 year old white male who presented findings of a patent ductus arteriosus, was operated upon elsewhere and no ductus was found. We believe that the case presented below is the first instance of an aortic septal defect diagnosed preoperatively by means of retrograde aortography, which was first introduced for visualization of the aorta and its branches, by Castellanos and Pereiras.[1]

Report of Case

M. P. was first seen at age of 3½ months on March 8, 1949 because of fever, rapid respirations and cough of several days' duration. A diagnosis of bronchopneumonia was made. Heart examination revealed the apex in the fifth left intercostal space, just outside the midclavicular line. There was a continuous murmur over the pulmonary area, which was transmitted towards the apex. The systolic murmur could also be heard over the second and third right intercostal spaces. Blood pressure was 90/15 in the upper extremities. Femoral pulsation was normal.

Fluoroscopic and roentgen-ray examinations performed after the bronchopneumonia had cleared, revealed a moderate enlargement of the transverse diameter of the heart with a straightening of the pulmonary area and with a definite hilar dance (fig. 1). The left oblique view (fig. 2) showed a moderate enlargement of the inflow tract of the left ventricle. An electrocardiogram (fig. 3) showed a left axis shift in the standard leads, a horizontally shaped heart in aV_L and aV_F and no evidences of heart strain in the precordial leads. A stethogram showed a continuous murmur in pulmonary area. (The stethogram was taken and read by Dr. A. Luisada.)

An angiocardiogram in the left oblique view showed reopacification of the pulmonary artery after the filling of the aorta; although these findings were compatible with the diagnosis of a patent ductus arteriosus, the presence of a systolic and diastolic murmur at such a young age (3½ months), and the recent experience with a 9 year old child who failed to show a patent ductus at operation, led us to believe that this patient might have an aortic septal defect. Since the patient was too young to have catheterization performed, and since catheterization does not differentiate aortic septal defect from patent ductus arteriosus, retrograde aortography was done. Five cc. of a 70 per cent Diodrast solution was injected into the left axillary artery and several films were taken. Figure 4 shows the dye entering the pulmonary artery from the aorta just above the semilunar valves. There is no evidence of a patent ductus arteriosus. A film, taken one second later, shows the entire heart filled with Diodrast.

From the Hektoen Institute of Medical Research, the Children's Department of the Cook County Hospital and the Department of Pediatrics of the University of Illinois College of Medicine. The study was supported by a grant from the Galter Foundation.

Read before the December 1949 meeting of the Chicago Heart Association and presented at the Scientific Exhibit, American Academy of Pediatrics, San Francisco, November, 1949.

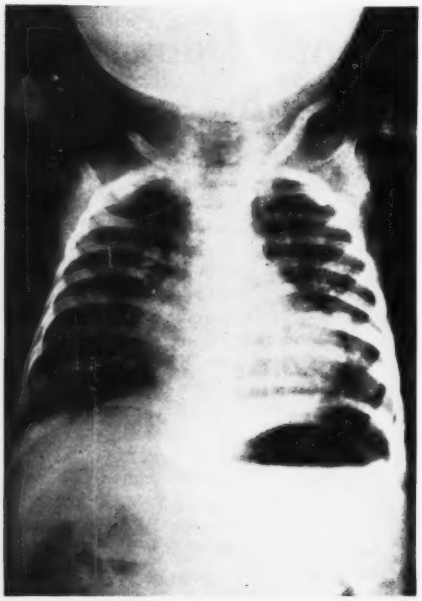

FIG. 1. Moderate enlargement of the transverse diameter of the heart in the posteroanterior view. Straightening of pulmonary area. Good vascular pulmonary markings.

FIG. 2. Left anterior oblique view. Moderate enlargement of the inflow tract of the left ventricle.

Because of these findings, an operation was not advised and the patient is being kept under observation.

DISCUSSION

A thorough review of the literature reveals 24 reported cases. As far as we could ascertain,

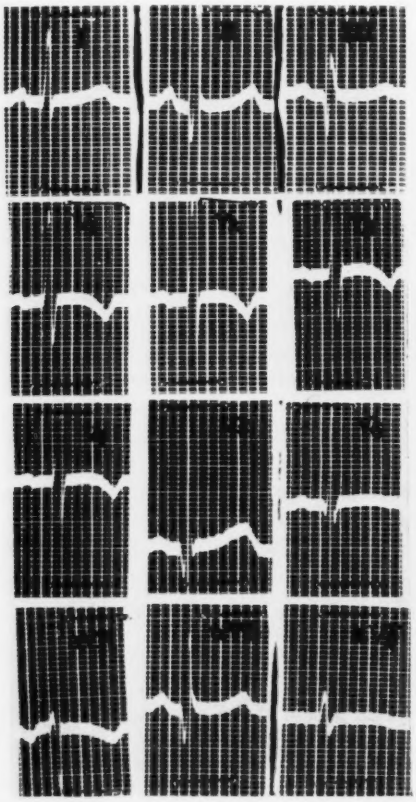

FIG. 3. Standard leads show a left axis deviation (important since patient was only 3½ months of age). Leads aV_L and aV_F show a horizontal position of the heart and the precordial leads show no evidences of heart strain.

no previously reported case was diagnosed clinically; the diagnoses were made either at autopsy or following surgery. Cotton and Hektoen[2, 3] reported the first case in the American literature in 1899 and 1900 and summarized the nine previously reported cases.[4–12] Since then 9 single cases have been reported.[13–21] Gibson, Potts and Langewisch[22] recently reported 4 cases in children, all of whom had

findings suggestive of patent ductus arteriosus, and in none was a patent ductus found at operation. Two of their cases had been catheterized previously and one had an angiocardiographic study done. The blood obtained from the pulmonary artery showed a significantly higher oxygen saturation than the blood from the right ventricle, and the angiocardiogram showed a refilling of the pulmonary artery after the dye entered the aorta; both of these findings

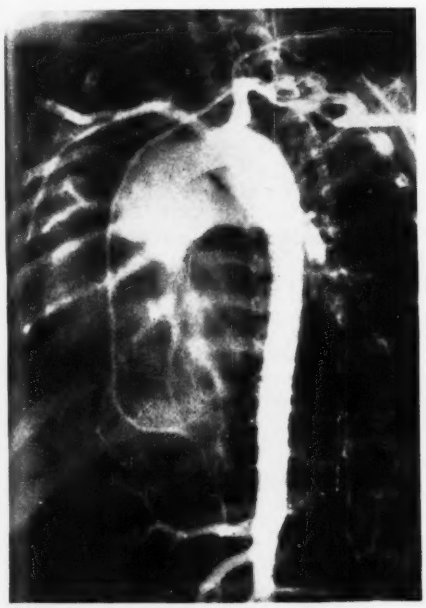

FIG. 4. Angiocardiogram obtained by retrograde aortography. Dye is seen entering the pulmonary artery from the aorta just above the semilunar valves. Note the semilunar valves, coronary artery and no evidences of a patent ductus arteriorus.

were considered strongly suggestive of a patent ductus and yet at operation none was found.

Anatomically, there exists a communication between the aorta and pulmonary artery a short distance above the semilunar valves; the communication is usually round or oval in outline and is 10 to 12 mm. in diameter. It is not in the location of the ductus arteriosus and is not to be considered as a short ductus, neither is it an aneurysm of the right sinus of Val-alva, which occasionally ruptures into the pulmonary artery, right auricle or right ventricle.

The hemodynamics of this rare lesion are very similar to that of a patent ductus arteriosus (fig. 5). Just as in the latter condition, blood is shunted from the aorta into the pulmonary artery and there is, therefore, no cyanosis. Systolic and diastolic murmurs may be heard in the pulmonary area and may be transmitted downwards. Although one may expect the continuous murmur to be located at a slightly lower level than that of a patent ductus

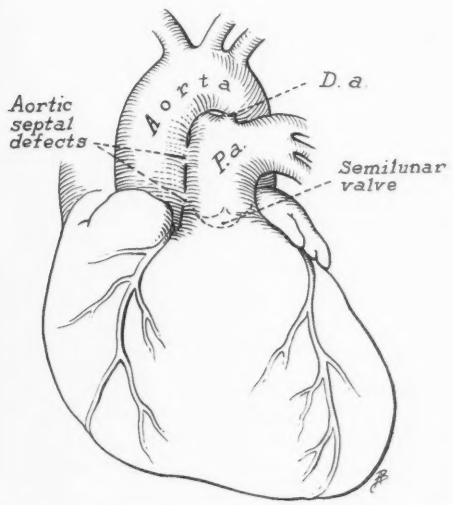

FIG. 5. Schematic drawing illustrating the reported locations of aortic septal defects. These sites are either just above the semilunar valves or at a higher level in the ascending aorta. The location of patent ductus arteriosus is also shown in order to emphasis the fact that the sites of the two anomalies differ.

arteriosus, and the diastolic murmur either may be missing or may not have the rumbling quality so characteristic of the murmur of patent ductus arteriosus, it has not been possible so far to differentiate the two; the character, location and duration of the murmur in the patent ductus arteriosus is subject to considerable variations. A wide pulse pressure may be present in both malformations. Fluoroscopic and x-ray examinations may reveal a prominent convexity in the pulmonary area and a hilar dance in either case. Angiocardiog-

raphy does not differentiate these two conditions because Sussman's sign (the localized bulging of the descending aorta in the region of the ductus just beyond the isthmus) is not always present and is furthermore not pathognomonic; and the indirect sign of reopacification of the pulmonary artery after the filling of the aorta may be present in either malformation. Even catheterization of the heart does not differentiate one anomaly from the other because the higher oxygen content of the blood obtained from the pulmonary artery as compared with that from the right ventricle occurs in either malformation. Differentiation of an aortic septal defect from a patent ductus arteriosus, is, however, of paramount importance because an aortic septal defect is usually not amenable to surgery. Patent ductus arteriosus can, of course, be easily corrected. As far as we know there is only one instance of successful surgical treatment of aortic septal defect.[24]

We believe that so far ours is the only reported case proved to have an aortic septal defect by retrograde aortography. As far as we know this appears to be the only method that may differentiate an aortic septal defect from a patent ductus arteriosus. Dexter[23] recently stated that, "venous catheterization is of little or no diagnostic value in anomalies of the aortic arch, but on one occasion aortic septal defect has been demonstrated by passage of the catheter from the pulmonary artery into the aorta, but in other suspected cases this could not be accomplished." Details on this case were not given by the author.

Summary

A case of an aortic septal defect in a $3\frac{1}{2}$ month old child is presented. The diagnosis was made by retrograde aortography.

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The Effect of Pancreatectomy on Lipemia, Tissue Lipidosis and Atherogenesis in Chicks

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Following complete pancreatectomy, chicks exhibit an excessive hypercholesterolemia when fed a diet containing cholesterol plus cottonseed oil. This inordinate hypercholesterolemia is accompanied by intensified atherogenesis, compared with unoperated controls on the same diet. Dietary neutral fat is essential for these excessive cholesterolemic and atherogenic responses. The possible significance of these findings for the pathogenesis of atherosclerosis in diabetic man is discussed.

ATHEROSCLEROSIS is the major unsolved therapeutic problem in diabetes mellitus today. This vascular "complication" is responsible for tremendous morbidity and mortality.[1]

Despite a mass of clinicopathologic data,[1] the causes for this "universality of atherosclerosis in diabetes"[2] remain obscure. Considerable evidence is extant implicating alterations in lipid metabolism in the pathogenesis of diabetic atherosclerosis.[1] Undoubtedly these data demonstrate an *association* between lipid derangements and atherogenesis in diabetes. However, the *precise relationship* of this lipid pathophysiology to diabetic atherogenesis remains an unsolved problem.

We undertook to investigate one aspect of this problem experimentally: the interrelationships among the pancreas, lipid metabolism and atherogenesis. Toward this end we studied the effect of pancreatectomy on lipemia, tissue lipidosis and atherogenesis in plain mash-fed, cholesterol-fed and stilbestrol-treated cockerels.

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METHODS

Two series* of chronic experiments were completed involving a total of 125 birds. The experimental regimens are indicated in table 1. Essentially, we assayed the effects of pancreatectomy on plasma and tissue lipid levels, and upon spontaneous and cholesterol-induced atherogenesis, in chicks maintained on one of four different diets: plain chick starter mash (PM—groups 1 and 2); mash supplemented with 2 per cent cholesterol and 5 per cent cottonseed oil (CO—groups 3 and 4); mash supplemented with 2 per cent cholesterol alone (C—groups 5 and 6); mash supplemented with 5 per cent cottonseed oil alone (O—groups 7 and 8). Groups 1, 3, 5 and 7 were pancreatectomized, groups 2, 4, 6 and 8 were unoperated controls. Hy-line cockerels were used throughout. One day old birds were obtained from a certified hatchery and reared in a battery brooder. During the initial five to seven weeks in the laboratory all chicks were maintained on tap water *ad libitum* and commercial chick starter mash of known composition.[1, 3] At age 5 to 7 weeks, pancreatectomy was performed under sodium pentobarbital anesthesia. Three to seven days postoperatively experimental and control groups were placed on their particular diets. Chicks were weighed weekly throughout the experiment and a record of feed intake was maintained. The duration of the study varied from 15 to 36 weeks (see tables 3 and 4). Birds were bled periodically from the alar vein. Aliquots of plasma were analyzed for lipid phosphorus, and for free and total cholesterol by the methods of Man and colleagues,[4, 5] and Schoenheimer and Sperry[6] respectively. At the end of the

* Dr. Raymond Harris, formerly of this department and now in Albany, N. Y., participated in the early phases of the series 1 experiments, and Dr. Ruth Pick in the later phases of the series 2 study.

experiment, surviving chicks were sacrificed by decapitation and exsanguination. At autopsy all the viscera were examined and the gross findings recorded. Completeness of pancreatectomy was confirmed in operated birds. The hearts and great vessels were carefully inspected for evidence of gross atheromatous plaques. Lesions, if any, were recorded graphically on special forms and graded grossly 0 to 4 according to criteria previously described.[1, 7] Specimens from different groups were indiscriminately mixed and graded consecutively as unknowns. Aortas from birds of series 1 and aliquots of liver from chicks of both series were analyzed for the various lipid fractions according to methods previously described.[3–6] Blocks of tissue were also taken for microscopic examination, fixed in aqueous formalin and stained with either Sudan IV (frozen sections) or hematoxylin-eosin (paraffin sections).

TABLE 1.—*Experimental Regimens*

Series	Group No.	No. of birds	Type of diet	Procedure	Diet		
					Plain mash	Cottonseed oil	Cholesterol
					%	%	%
1	1	10	PM*	Panc.†	100	0	0
	2	20	PM	None	100	0	0
	3	5	CO*	Panc.	93	5	2
	4	5	CO	None	93	5	2
	5	5	C*	Panc.	98	0	2
	6	10	C	None	98	0	2
2	1	10	PM	Panc.	100	0	0
	2	10	PM	None	100	0	0
	3	10	CO	Panc.	93	5	2
	4	15	CO	None	93	5	2
	5	10	C	Panc.	98	0	2
	6	5	C	None	98	0	2
	7	5	O*	Panc.	95	5	0
	8	5	O	None	95	5	0

* PM = plain mash
CO = mash enriched with cholesterol plus cottonseed oil
C = mash enriched with cholesterol alone
O = mash enriched with cottonseed oil alone
† Panc. = pancreatectomy

In addition to these chronic experiments in the chick, the effect of pancreatectomy on the avian plasma lipid response to estrogens[1, 8–12] was assayed in two further groups of 5 birds each, studied concurrently with series 1. One group was pancreatectomized, and the other unoperated (groups 9 and 10). Both groups subsisted on plain mash and were implanted subcutaneously with 25 mg. pellets of diethylstilbestrol† at intervals of three weeks for a period of 35 weeks. The number of birds surviving to the end of the experiment was inadequate to evaluate the effect of pancreatectomy on estrogen-induced atherogenesis.

† The pellets of diethylstilbestrol were generously supplied by Dr. Kenneth G. Kohlstaedt of Eli Lilly & Co., Indianapolis, Ind.

RESULTS

Since the biochemical and morphologic findings in the two series of studies were essentially similar, they have been combined for presentation.

A. Feed Intake and Weight Change. All groups of depancreatized chicks (table 1) exhibited normal feed consumption and rate of gain in weight, compared with their unoperated paired controls. In contrast to reported findings in the duck,[13] pancreatectomy was not followed by weight loss in cockerels. The depancreatized birds had grossly normal excreta throughout. steatorrhea was not observed.

All birds, pancreatectomized and normal, subsisting on various types of supplemented mash (groups 3 to 8) consistently exhibited normal feed intake and weight change. No gross signs of nutritional deficiency were noted at any time. Thus the experimental diets were apparently without deleterious effects nutritionally.

B. Plasma Glucose and Lipid Levels. In accord with previous reports,[13–16] pancreatectomy was without sustained effect on plasma or blood glucose levels in the chick. Intravenous glucose tolerance tests* on fed birds revealed essentially similar curves for normal and depancreatized chicks. None of the experimental diets affected the blood glucose level or the glucose tolerance curves in pancreatectomized or normal cockerels, regardless of concomitant induced hyperlipemia. Apparently neither cholesterol, nor cottonseed oil, nor the two in combination in the diet affected carbohydrate metabolism, as assayed by the foregoing tests. Further, the normal and depancreatized cockerels fed plain mash and implanted with

* We appreciate the cooperation of Dr. Samuel D. Loube, formerly of the Department of Metabolic and Endocrine Research, now in Washington, D. C., who participated with us in accomplishing some of these tests. B. Huddleston of the Department of Metabolic and Endocrine Research assisted us by performing some of the plasma glucose determinations for this study. We gratefully acknowledge her cooperation in this project.

diethylstilbestrol pellets (groups 9 and 10) also had glucose levels essentially similar to the controls (groups 1 and 2) (cf.[18]).

Pancreatectomized chicks subsisting on plain mash alone exhibited normal plasma cholesterol and phospholipid levels throughout the experiment (groups 1 and 2, table 2). These determinations yielded no evidence of a chronic disturbance in lipid metabolism in normally fed, depancreatized cockerels.

Operated birds eating a diet of mash supplemented with 2 per cent cholesterol and 5 per cent cottonseed oil exhibited a pattern of plasma lipid levels significantly different quantitatively from their paired controls (groups 3 and 4, table 2). Throughout the experiment in both series, the pancreatectomized birds (group 3) responded to this diet with a far more severe hypercholesterolemia (1310 mg. per 100 cc. mean total cholesterol concentration for the duration of the experiment, group 3; vs. 619, group 4—table 2). Both groups had only a moderate hyperphospholipemia, similar in degree. In accord with previous experience in cholesterol-fed chicks,[1, 17-20] the increment in plasma total cholesterol markedly exceeded that in lipid phosphorus. Hence the ratio of plasma total cholesterol to lipid phosphorus rose several fold, this alteration being significantly more marked in the depancreatized chicks (table 2).

TABLE 2.—*Mean Plasma Lipid Levels, Series 1 and 2 Combined*

Group	Determination	Weeks on Diet							Mean§	Mean C:P‖
		1	3	5	10	15	20	30		
1	T. Chol.*	151	102	109	98	126	112	74‡	110	14.5
	Lipid P*	7.3	6.9	9.1	7.4	6.6	8.4	—	7.6	
2	T. Chol.	115	110	84	113	75	127	135‡	108	14.2
	Lipid P	6.9	8.1	7.7	7.0	8.2	8.5	—	7.6	
3	T. Chol.	485	1419	1315	1520	1790	—	—	1310	78.4
	Lipid P	9.8	16.3	18.7	19.5	19.3	—	—	16.7	
4	T. Chol.	332	412	655	814	882	—	—	619	44.9
	Lipid P	9.0	16.8	13.6	14.3	15.4	—	—	13.8	
	T. Chol.	210	426	533	700	666	—	—	507	50.7
	Lipid P	7.0	10.3	11.5	10.4	11.0	—	—	10.0	
6	T. Chol.	431	420	361	475	463	—	—	430	38.4
	Lipid P	10.8	12.7	10.6	11.3	10.7	—	—	11.2	
7	T. Chol.†	87	—	80	88	76	—	—	83	—
	Lipid P	—	—	—	—	—	—	—	—	
8	T. Chol.†	92	—	89	83	75	—	—	85	—
	Lipid P	—	—	—	—	—	—	—	—	
9†	T. Chol.	299	106	216	733	606	1125	—	514	9.1
	Lipid P	19.5	11.4	25.1	14.9	73.0	193.0	—	56.2	
10†	T. Chol.	226	133	474	827	800	804	—	544	7.9
	Lipid P	31.3	12.8	47.8	135.0	99.4	86.3	—	68.8	

* T. Chol. = total cholesterol in mg. per 100 cc.
Lipid P = lipid phosphorus in mg. per 100 cc.
† Series 1 only
§ Mean = average over entire experiment
‖ C:P = ratio of total cholesterol to lipid phosphorus
‡ Series 2 only

In contrast to these findings, pancreatectomized birds fed a mash supplemented with 2 per cent cholesterol (no cottonseed oil) had a plasma lipid pattern essentially similar to that of their unoperated paired controls (groups 5 and 6, table 2). Thus groups 4, 5 and 6 resembled each other closely with respect to degree of hypercholestolemia and hyperphospholipemia. This was observed in both series. Without oil in the diet, depancreatized chicks apparently exhibited a response to cholesterol feeding quantitatively different from operated birds given cholesterol and oil.

Pancreatectomized and normal cockerels fed a mash supplemented with 5 per cent cottonseed oil exhibited normal plasma cholesterol concentrations throughout (groups 7 and 8, table 2).

None of the foregoing eight experimental groups had any alteration in the ratio of plasma free to total cholesterol. No consistent differences were noted between depancreatized and unoperated chicks in their plasma lipid response to repeated diethylstilbestrol pellet implantations (groups 9 and 10, table 2).

TABLE 3.—*Mean Tissue Lipid Levels, Series 1 and 2 Combined*

Group	Weeks on diet	Organ	Lipid P mg. per 100 Gm.	Total cholesterol mg. per 100 Gm.	Free cholesterol mg. per 100 Gm.	Total fatty acids mg. per 100 Gm.
1*	15–17	Liver	100	370	294	3180
2*	15–17	Liver	85.6	287	277	5340
1†	36	Liver	98.8	353	310	2405
2†	36	Liver	97.3	318	300	2368
3*	15–17	Liver	88.7	1330	584	4920
4*	15–17	Liver	113	2860	1260	1600
5*	15–17	Liver	113	2380	1010	4420
6*	15–17	Liver	127	3130	1006	5050
1*	15–17	Aorta	28.1	181	165	—
2*	15–17	Aorta	33.8	174	168	—
3*	15–17	Aorta	31.0	455	256	—
4*	15–17	Aorta	30.6	423	256	—
5*	15–17	Aorta	25.1	312	210	—
6*	15–17	Aorta	36.6	285	211	—

* Series 1 chicks
† Series 2 chicks

TABLE 4.—*Summary of Gross Grading of Aorta Lesions of Chicks in Series 1 and 2*

Group	Weeks on diet	No. of birds	No. with lesions	Per cent with lesions	No. with lesions grade 1 or >	Per cent with lesions grade 1 or >	Av. grading of birds with lesions
1	36	13	6	46	6	46	1.6
2	36	12	4	33	2	17	0.4
3	15–17	13	13	100	12	92	3.6
4	15–17	16	15	94	12	75	2.3
5	15–17	12	10	83	8	67	1.8
6	15–17	8	7	88	7	88	1.9
7	15	3	2	67	0	0	0.3
8	15	3	3	100	1	33	0.6

C. Tissue Lipid Levels. Pancreatectomy failed to result in the development of a fatty liver in chicks fed plain mash (groups 1 and 2, table 3). With cholesterol feeding, the degree of hepatic cholesterosis tended to be less in the operated birds (groups 3 to 6, table 3). No other consistent differences in liver lipids were noted among these groups.

Pancreatectomy had no significant effect on aorta cholesterol concentration in chicks fed either plain mash or cholesterol (table 3). In accord with previous experience,[1, 17-20] cholesterol feeding (with or without cottonseed oil) induced an increase in aorta cholesterol concentration. This increment was similar in degree in depancreatized and unoperated birds. No significant changes from normal in aorta phospholipid concentration were recorded in these cholesterol-fed cockerels (groups 3 to 6, table 3).

D. Morphologic Findings. In most operated birds, autopsy confirmed the completeness of pancreatic extirpation. A few chicks showed remnants of this organ.

Findings in the aortas and great vessels are summarized in table 4. Despite normal plasma lipid levels in depancreatized chicks fed plain mash, these birds exhibited a slightly higher incidence and a markedly greater severity of atherosclerotic lesions of the spontaneous type[1] after 36 weeks on diet (groups 1 and 2, table 4).* No birds, operated or controls, in either plain mash fed group had gross lesions of the induced type[1] in the thoracic aorta.

In conjunction with the more severe hypercholesterolemia and elevation of the plasma total cholesterol:lipid phosphorus ratio, pancreatectomized cockerels fed mash supplemented with 2 per cent cholesterol and 5 per cent cottonseed oil had significantly more severe cholesterol-induced atherosclerosis.† Greater se-

* This is one of few studies[1] in which the incidence and severity of chick spontaneous atherosclerosis has been influenced in an apparently significant manner by an experimental procedure. Additional investigations are indicated to test this phenomenon further. Our limited knowledge of the pathogenesis of the spontaneous lesion in the chick[1] renders its evaluation difficult.

† These data alone do not permit an evaluation as to the relative roles of hypercholesterolemia per se compared with elevated plasma total cholesterol:lipid phosphorus ratio in contributing to atherogenesis.[1]

verity of atherosclerosis in chicks of group 3 compared with group 4 could not be correlated with either liver or aorta lipid values of these birds (tables 3 and 4).

In conjunction with their similar degrees of hyperlipemia, cholesterol-fed chicks of groups 5 and 6 had a similar incidence and severity of atherosclerosis. Unlike chicks fed cholesterol and cottonseed oil mash (group 3), birds subsisting on cholesterol mash without oil (group 5) exhibited no effect of pancreatectomy on atherogenesis.

Feeding mash supplemented with 5 per cent cottonseed oil for 15 weeks had no significant influence on either plasma cholesterol levels or spontaneous atherogenesis in pancreatectomized cockerels (groups 7 and 8, tables 2 and 4). Both groups of oil fed chicks, depancreatized and unoperated, were uniformly free of atherosclerotic plaques of the cholesterol-induced type in the thoracic aorta.

Discussion

Our findings in this study demonstrated the existence of subtle defects in lipid metabolism in depancreatized cockerels. These defects were brought out particularly by a diet of mash enriched with cholesterol plus cottonseed oil. On this regimen pancreatectomized chicks exhibited an inordinate hypercholesterolemic response. Increased incidence and severity of atherosclerotic lesions accompanied this excessive hypercholesterolemia. Thus the lipid metabolic defects in depancreatized cockerels were associated with, and apparently related to, intensified atherogenesis. Hence in the chick—as in man—the pancreas apparently influences the metabolism of lipids related to atherogenesis. This biologic similarity emerges despite initial data indicating that pancreatic deficiency in chick and man has fundamentally different effects on lipid metabolism.

Concurrent studies in our laboratory by Stamler and Pick demonstrated that similar subtle defects in carbohydrate metabolism were present in masked form in pancreatectomized and alloxanized cockerels.[21] These birds, with normal fasting blood glucose levels, exhibited inordinate hyperglycemic responses to adrenal cortical extract (ACE).* Gluconeogenesis induced by adrenal cortical extract apparently overwhelmed limited glucose regulatory mechanisms in these chicks. Corresponding to their lack of pancreatic β cells, these depancreatized or alloxanized cockerels apparently had a relative insulin lack (latent diabetic or subdiabetic tendency).[21-23]

Together with the lipid data of the present experiment, these findings indicate that chicks are not so fundamentally dissimilar from mammals (dog, rabbit, rat, man)† in carbohydrate and lipid metabolism as one might conclude from initial study of a pancreatectomized preparation. The apparent differences between man and chick may not necessarily be qualitative ones, but rather at least in part quantitative.

The data of the present study further demonstrated significant effects of dietary neutral fat ingestion on cholesterolemia and atherogenesis in cholesterolized, depancreatized chicks. On a 2 per cent cholesterol mash without cottonseed oil, pancreatectomized and unoperated cockerels exhibited similar cholesterolemic and atherogenic responses. With the incorporation of 5 per cent cottonseed oil in the 2 per cent cholesterol mash, operated and control birds manifested significantly different responses.‡ This finding is generally in agreement with work indicating that neutral fat ingestion may in some circumstances influence cholesterolemia and atherogenesis in man, whereas in other instances it may be without effect.[1, 24-32] The factors responsible for these phenomena are as yet obscure.

The present experiment could not yield data indicating the mechanisms of the altered cholesterolemic and atherogenic responses of de-

* This production of marked hyperglycemia with adrenal cortical extract in pancreatectomized or alloxanized chicks makes available a preparation more closely similar to diabetic man. Studies on lipid metabolism and atherogenesis in this preparation are being pursued in this laboratory.

† Elsewhere we have reviewed the findings in these mammalian species on the interrelationships among the pancreas, lipid metabolism and atherogenesis.[1]

‡ In contrast, addition of 5 per cent cottonseed oil to plain mash, devoid of a cholesterol supplement, had no effect on lipemia or atherogenesis in normal or depancreatized cockerels.

pancreatized cockerels to cholesterol-cottonseed oil mash. Further studies on this problem are currently in progress in our laboratory.[1]

Summary

Pancreatectomized chicks exhibit an excessive hypercholesterolemia when fed a diet containing cholesterol plus cottonseed oil. This inordinate hypercholesterolemia is accompanied by intensified atherogenesis, compared with unoperated controls on the same diet.

Neutral fat is essential for these excessive cholesterolemic and atherogenic responses, since they are absent in depancreatized cockerels fed mash supplemented only with cholesterol (i.e. without oil).

Plain mash-fed pancreatectomized cockerels exhibit intensified spontaneous atherogenesis, although they have normal plasma lipid and glucose levels.

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Effects of Desoxycorticosterone Acetate on Cholesterolemia, Blood Pressure and Atherogenesis in Chicks

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Chronic exhibition of chicks to desoxycorticosterone acetate produces a slight but definite rise in blood pressure. This effect is increased by addition of salt to the diet. This regimen does not affect cholesterol levels and atherogenesis in the chick on ordinary mash. However, in the presence of a mildly atherogenic diet (0.25 per cent cholesterol) concomitant DCA exhibition increases the incidence and severity of atherosclerosis.

SEVERE atherosclerosis is a significant "complication" in clinical hyperadrenocortical states, for example in Cushing's syndrome.[1,2] These diseases are rare. However, many of their features are readily produced by overdosage with adrenocorticotropic hormone (ACTH) or corticosteroids (cortisone, desoxycorticosterone, and others). These endocrine preparations are now being extensively used in clinical therapeutics. The problem arises: will atherosclerosis supervene as a complication in patients treated with these drugs?

The possibility of this untoward development is emphasized by recent clinical observations indicating that therapy with cortisone effects a rise in plasma cholesterol concentration.[3] It is further highlighted by laboratory data demonstrating that desoxycorticosterone and other steroids may induce hypertension and arteriolonephrosclerosis* in experimental animals.[4–7]

These facts emphasize the need for investigations clarifying the relationships between adrenal corticoids and atherogenesis. Towards this end, we studied the effects of the mineralocorticoid, desoxycorticosterone acetate (DCA),† on cholesterolemia, blood pressure and atherogenesis (spontaneous and cholesterol-induced) in cockerels.

Methods

Two series of experiments were completed. In both, 1 day old Hy-line cockerels were obtained from a certified hatchery and reared in a battery brooder. A total of 200 birds were used in these studies (table 1). Daily intramuscular administration of DCA was begun when the chicks were 1 week old. The initial daily dosage of DCA was 1 mg.; this was progressively increased during the experiment to a maximum of 4 mg. The experimental dietary regimens are indicated in table 1. Essentially, with these regimens the effects of DCA were studied in two sets of paired groups (groups 1 and 2, and groups 3 and 4), fed mashes respectively with and without a cholesterol-oil supplement. In series I, these experimental diets were initiated when the birds were 4 weeks old. Until then, all groups subsisted on a commercial chick starter mash (plain mash) of known composition.[1,8] In series II, the diets indicated in table 1 were fed beginning with the first day of life. In series II, the effects of DCA were analyzed in chicks fed a cholesterol-oil mash containing a dosage of sterol (0.25 per cent) known to induce a minimal hypercholesterolemia and organ lipidosis,[1,9] in contrast to series I wherein a relatively high dosage of sterol (2 per cent) was given. Further, in series II a supplement of 1 per cent sodium chloride was added to the mash of all four experimental groups in order to enhance the hypertensive effect of DCA in the two groups receiving

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* Atherosclerosis has not been reported in these animals.

† We wish to express our appreciation to Dr. W. Alan Wright of the Schering Corp., Bloomfield, N. J., who supplied us with generous amounts of desoxycorticosterone acetate in oil (Cortate, Schering).

the steroid.[5, 10] In both series, birds received mashes and tap water freely.

In both series, chicks were weighed weekly throughout the experiment and a record of feed intake was maintained. At intervals, data on water intake were also collected. In order to assay the role of dietary sodium in the pathogenesis of DCA-induced hypertension[4–7, 10] and polydypsia,[11–13] two additional groups of 5 chicks each were fed a low-sodium diet (Lonalac*) during the fifth to twentieth weeks of life. One of these groups was given DCA in doses similar to those used in series I and II. This aspect of the study was carried out concurrently with the series II experiment.

At intervals throughout both series of experiments, blood was drawn from an alar vein or by direct cardiac puncture. Aliquots of heparinized plasma from individual birds were analyzed for total cholesterol by the method of Schoenheimer and Sperry.[14] In both series, blood pressures were also determined at five-week intervals in unanesthetized quiescent birds by direct puncture of a sciatic artery, isolated by cut-down. Mean blood pressures were read on a mercury manometer. In series I, comb size indexes were estimatde at five-week intervals, utilizing established methods of measurement and calculation.[15]

In series I, chicks were sacrificed by decapitation and exsanguination when 15 weeks of age, after 14 weeks on DCA and 11 weeks on the experimental diets. In series II, birds were sacrificed when 5, 10 and 15 weeks of age. At autopsy all the viscera were examined and the gross findings recorded. The hearts and great vessels were carefully inspected for gross atherosclerotic plaques. Established methods and precautions were utilized in grading these lesions.[1] Adrenals of both series were pooled by group and weighed post mortem; total body weight and heart weight of individual birds were also obtained. Blocks of tissue were then fixed in 10 per cent aqueous formalin and subsequently stained with hematoxylin-eosin (paraffin sections), Sudan IV (frozen sections), and Van Giesson or Masson connective tissue stain (paraffin sections).

Results

Feed Intake and Weight Gain. In both series, DCA-treated birds exhibited feed intakes and rates of weight gain similar to their paired control groups. All groups on experimental regimens corresponded to the plain mash-fed controls (group 1, series I and group 5, series II—table 1) in these respects. Hence any observed group differences in atherogenesis cannot be attributed to differences in development or in ingestion of experimental regimens.[1]

Water Intake. In both series, respectively with (series II) and without (series I) a supplement of 1 per cent sodium chloride in the mash, chicks given DCA exhibited polydypsia (table 2). In contrast, DCA-treated birds subsisting on a low sodium diet (Lonalac) exhibited no polydypsia, compared with their paired controls

Table 1.—*Experimental Regimens*

Series	No. of chicks	Plain mash	Cholesterol	Cottonseed oil	Sodium chloride
		%	%	%	%
I. Group 1—PM	20	100	0	0	0
I. Group 2—PM + DCA	12	100	0	0	0
I. Group 3—C-O	12	93	2	5	0
I. Group 4—C-O + DCA	12	93	2	5	0
II. Group 1—SM	30	99	0	0	1
II. Group 2—SM + DCA	30	99	0	0	1
II. Group 3—C-O-S	30	93.75	0.25	5	1
II. Group 4—C-O-S + DCA	30	93.75	0.25	5	1
II. Group 5—PM	24	100	0	0	0

PM = Plain mash.
C-O = 2% Cholesterol–5% Oil mash.
SM = Plain mash supplemented with 1% NaCl.
C-O-S = 0.25% Cholesterol–5% Oil mash supplemented with 1% NaCl.
In series 2, the dosage of salt was 0.5% during the first 5 weeks of the experiment; thereafter it was 1%, as indicated above.

Table 2.—*Effect of DCA on Water Intake (cc. per chick per day)*

	Group 1—PM	Group 2—PM + DCA	Group 3—C-O	Group 4—C-O + DCA
Series I*	156	308	179	283
Series II†	320	499	343	580

For symbols see table 1.
* Data collected during eighth week on DCA (chicks 9 weeks old).
† Mash of all four groups supplemented with 1% NaCl; data collected during eighth week on DCA (chicks 9 weeks old).

* We gratefully acknowledge the assistance of Dr. Warren M. Cox, Jr. of Mead Johnson and Co., Evansville, Indiana, who contributed generous supplies of Lonalac for this and other projects.

receiving no corticoid.*[11, 16] Thus during their seventh week on DCA, Lonalac-fed cockerels (12 weeks of age) ingested 300 cc. of water per bird per day; Lonalac controls not given DCA ingested 292 cc.

Cholesterolemia. Data on plasma cholesterol levels are summarized in table 3. In both series, DCA-treated chicks subsisting on mash without a cholesterol supplement (group 2) exhibited normal plasma cholesterol levels throughout. DCA-treated birds fed mash containing cholesterol and oil (group 4) had a hypercholesterolemia similar in degree to their paired controls receiving no steroid. This was true in both series, with 2 per cent and 0.25 per cent cholesterol supplement respectively. In series II, birds subsisting on the 0.25 per cent cholesterol mash beginning with the first day of life, did not develop a definitive minimal hypercholesterolemia[9] until the latter weeks of the experiment (table 3). This hypercholesterolemia was slightly, but not significantly greater in the DCA-treated chicks (series II–group 4), compared with their paired controls (series II–group 3), not receiving steroid. Apparently DCA was without definitive, significant effect on cholesterolemia in cockerels fed a diet with or without a cholesterol supplement.

TABLE 3.—*Effect of DCA on Cholesterolemia*

Series	Weeks on Experimental Diet							Mean for Duration of Experiment
	1	3	5	8	10	12	15	
Mean Plasma Total Cholesterol in mg.%								
I. Group 1	92	94	117	—	98	—	—	100
I. Group 2	92	102	90	—	105	—	—	97
I. Group 3	476	979	1471	—	966	—	—	973
I. Group 4	621	875	1125	—	1517	—	—	1035
II. Group 1	—	—	87	78	89	83	113	90
II. Group 2	—	—	100	103	94	90	103	98
II. Group 3	—	117	100	123	109	175	217	140
II. Group 4	—	126	107	145	151	196	244	162

See table 1 for experimental regimens.

TABLE 4.—*Effect of DCA on Mean Blood Pressure*

	Weeks on DCA		
	5	10	15
	mm. Hg	*mm. Hg*	*mm. Hg*
I. Group 1	—	111	123
I. Group 2	—	126	142
I. Group 3	—	126	128
I. Group 4	—	122	130
II. Group 1	135	152	153
II. Group 2	157	165	178
II. Group 3	142	148	148
II. Group 4	156	164	172
II. Group 5	134	133	129

Blood Pressure. Data on mean blood pressures are summarized in table 4. In series I, DCA chicks on plain mash (group 2) had slightly higher mean blood pressures than their paired controls (group 1). DCA birds fed 2 per cent cholesterol–5 per cent oil mash in this series (group 4) exhibited blood pressures almost identical with those of their paired controls (group 3).

In series II, with addition of 1 per cent sodium chloride to the experimental diets of all groups, the DCA-treated cockerels consistently exhibited mean blood pressures greater than those of their paired controls. The DCA-induced increments in blood pressure became progressively greater with prolongation of the experiment (table 4). Addition of salt to the diet effected a slight blood pressure elevation in birds not receiving DCA (compare groups 1 and 3 with group 5, table 4).[10]

In contrast to this rise in mean blood pressure in DCA chicks having access to salt in their diets, DCA-treated cockerels on a low sodium diet (Lonalac) failed to develop any increment in arterial pressure.[16] Thus after seven weeks on DCA plus Lonalac, birds had a mean pressure of 133 mm. Hg (cf. group 5, table 4), compared with a value of 147 mm. Hg for their paired controls subsisting on Lonalac without DCA.

Our data fail to indicate any consistent tendency for cholesterol feeding to elevate the blood pressure of chicks.[1,17–26] In series I, cockerels fed 2 per cent cholesterol–5 per cent oil mash (group 3) did have slightly higher mean blood pressures than birds subsisting on plain mash (group 1). However, in series II, chicks with and without a cholesterol supplement in their

* Both groups of chicks fed Lonalac exhibited diminished feed intake, growth and development.

diets (groups 3 and 1) had similar blood pressures (table 4).

Atherosclerotic Lesions. The gross findings in the great vessels are summarized in table 5. In both series, no chicks subsisting on mash without a cholesterol supplement exhibited lesions in the thoracic aorta (groups 1 and 2). In such cockerels, DCA failed to induce lesions in this area, the site of predilection for atherosclerosis of the cholesterol-induced type.[1]

At 14 to 15 weeks of age in both series, birds eating feed devoid of cholesterol supplement had atherosclerotic lesions of the spontaneous type[1] in the abdominal aorta (groups 1 and 2). In both series, DCA-treated birds on this diet had slightly, but not significantly, greater incidence and severity of such abdominal aorta spontaneous lesions.

In series I, a diet of 2 per cent cholesterol–5 per cent cottonseed oil mash for 11 weeks induced severe atherogenesis in both groups 3 and 4, with and without DCA (table 5). The incidence and severity of cholesterol-induced atherosclerosis in both the thoracic and abdominal aorta were similar in these two groups. The possibility presented itself that the atherogenesis occurring with this cholesterol dosage was of such intensity as to mask any aggravating effect of DCA. Hence in series II, we utilized the lower cholesterol dosage (0.25 per cent), with which minimal hypercholesterolemia and mild atherogenesis develop. With this second dietary regimen, chicks with and without DCA exhibited no significant differences in atherogenesis when sacrificed after 5 and 10 weeks of experimental feeding (4 and 9 weeks of DCA treatment for group 4, table 5). However, after 15 weeks on the 0.25 per cent cholesterol–5 per cent oil dietary regimens, the DCA-treated cockerels (group 4) had significantly greater incidence and severity of lesions in both thoracic and abdominal aorta segments (table 5). This more intensified atherogenesis in the birds receiving DCA plus 0.25 per cent cholesterol during the last period of the experiment corresponded in time with their development of maximal blood pressure increments. It also corresponded in time with their development of a minimal hypercholesterolemia, which was slightly greater in degree in these DCA-treated

TABLE 5.—*Effects of DCA on Spontaneous and Cholesterol-Induced Atherogenesis*

	Duration of experimental feeding	% with lesions in thoracic aorta	% with lesions in abdominal aorta	% with lesions in thoracic aorta grade 1 or >	% with lesions in abdominal aorta grade 1 or >	Mean gross grading of lesions in birds with lesions		Mean gross grading of lesions—whole aorta—all birds
						Thoracic aorta	Abdominal aorta	
	weeks							
I. Group 1	10	0	35	0	0		0.4	0.1
I. Group 2	10	0	50	0	0	0	0.6	0.3
I. Group 3	10	100	100	100	88	2.4	1.3	3.7
I. Group 4	10	100	100	100	75	2.9	1.3	4.2
II. Group 1	5	0	0	0	0	0	0	0
II. Group 2	5	0	0	0	0	0	0	0
II. Group 3	5	13	0	0	0	0.3	0	<0.1
II. Group 4	5	0	0	0	0	0	0	0
II. Group 1	10	0	0	0	0	0	0	0
II. Group 2	10	0	0	0	0	0	0	0
II. Group 3	10	25	13	13	0	0.6	0.3	0.2
II. Group 4	10	25	25	13	0	1.0	0.5	0.4
II. Group 1	15	0	33	0	0	0	0.3	0.1
II. Group 2	15	0	57	0	14	0	0.5	0.3
II. Group 3	15	17	50	0	0	0.1	0.4	0.3
II. Group 4	15	45	91	9	18	0.3	0.5	0.7

cockerels than in their paired controls (series II–groups 3 and 4, table 3).

Heart and Adrenal Weights, and Comb Size Indexes. In accordance with the elevations in blood pressure they tended to exhibit, all DCA-treated groups in both series had increased heart weights and wet heart weight:wet body weight ratios (table 6). Determinations of dry heart weight revealed that the foregoing alterations were attributable to a true increase in cardiac muscle mass (hypertrophy).

Corresponding to previous work in other species,[27, 28] DCA-treated cockerels, with and without cholesterol in the diet, exhibited hypoplasia of the adrenals. Thus in series I, the adrenals of groups 1 and 2 weighed 95 and 65 mg. respectively; of groups 3 and 4, 98 and 72 mg. (groups 2 and 4 received DCA). From studies in other laboratories, it would appear that this adrenal hypoplasia may be a result of pituitary hypoadrenocorticotropism, occurring secondary to administration of exogenous steroid.[29] *

TABLE 6.—*Effects of DCA on Heart Weight*

	Mean wet body weight	Mean wet heart weight	Mean dry heart weight	Wet heart / Wet body	Dry heart / Wet heart
	Gm.	*Gm.*	*Gm.*		
I. Group 1..	1560	7.68	1.66	.49	.22
I. Group 2..	1543	9.35	2.72	.61	.29
I. Group 3..	1581	7.94	1.89	.50	.24
I. Group 4..	1686	10.52	2.69	.62	.26
II. Group 1..	1546	6.84	1.53	.44	.22
II. Group 2..	1520	11.12	2.58	.73	.23
II. Group 3..	1760	7.15	1.72	.41	.24
II. Group 4..	1364	10.24	2.00	.75	.20

I = series 1, 15 week sacrifice.
II = series 2, 15 week sacrifice.

DCA-treated chicks had low comb size indexes compared with their paired controls. Thus in series I cockerels, 12 weeks of age, groups 1 and 2 had comb size indexes of 30 and 16 units respectively; groups 3 and 4, 30 and 12. These data indicate that DCA administration was associated with decreased androgenic activity.[15]

Other Morphologic Findings. Microscopic sections of the kidneys of DCA-treated chicks, groups 2 and 4 in both series, revealed moderate arteriolar thickening. This was due to increased deposition of fibrous tissue in the outer layers of the media and in the adventitia. Intimal thickening was not observed. Moderate focal interstitial fibrosis was demonstrable by connective tissue stains. Amorphous basophilic material was deposited between the glomerular capillaries. Glomerular enlargement, hypertrophy of the parietal cells of Bowman's capsule, and changes in the epithelial lining cells of the proximal convoluted tubules[4, 5] were not prominent findings. Hyalinized glomeruli, hyaline tubular casts and hyalinized necrosis of arteriolar walls were not seen.[4, 5]

DISCUSSION

The data from both series of experiments clearly indicate that chronic administration of desoxycorticosterone acetate has little or no intensifying effect on the spontaneous atherogenesis of chicks. Moreover, in birds subsisting on a mash devoid of a cholesterol supplement, DCA fails to induce atherosclerotic plaques of the cholesterol-induced type[1] in the thoracic aorta. These cockerels are uniformly free of such lesions. These negative results were obtained despite the definite increases in blood pressure occurring in DCA-treated chicks. These observations are in accord with our previous findings on the influence of salt hypertension on atherogenesis in birds fed mash lacking a cholesterol supplement.[30] They constitute further evidence that hypertension, per se, does not influence atherogenesis, when it is not accompanied by an alteration in lipid and cholesterol metabolism.[1, 17, 19, 30–32]

Several factors may account for the apparently discrepant results between Series I and Series II with respect to the influence of DCA on cholesterol-induced atherosclerosis:

* Operation of this mechanism in the chick remains to be demonstrated. In our laboratory Stamler and associates, have been unable to record changes in blood glucose levels or white blood cell counts (including eosinophils) in chicks treated acutely with 5 mg. doses of mammalian ACTH. Others[2] obtained similar negative results, indicating that the avian adrenal cortex is not stimulated by mammalian ACTH. To our knowledge, no studies have been accomplished on avian anterior pituitary preparations and their corticotropic activity.

the failure of DCA to intensify atherogenesis in series I* may be due to the absence of a definitive blood pressure elevation in these birds. It may also be attributed to the lack of any consistent effect of DCA on cholesterolemia in cockerels fed a mash supplemented with 2 per cent cholesterol plus 5 per cent cottonseed oil. As already indicated, it is further possible that cholesterol-induced atherogenesis was so severe with this dietary regimen as to mask any intensifying effect of DCA.

With the lower cholesterol dosage of series II, a definite, significant influence of DCA on atherogenesis was demonstrated. This intensifying effect of DCA on cholesterol-induced atherogenesis was clearcut, but not gross or extreme. It may be a by-product of the slightly greater hypercholesterolemia of these DCA-treated birds, compared with their paired controls. It may also be related to the DCA-induced blood pressure elevation, which in the presence of increased plasma cholesterol concentration may intensify atherogenesis.[1, 17, 19, 30–32, 34–36] Further, this effect of DCA on atherogenesis in chicks fed 0.25 per cent cholesterol–oil mash may be due to possible specific effects of the hormone on vascular tissue[1, 17, 37] or on plasma cholesterol-bearing colloidal lipoprotein micelles.[1, 38] Finally, it may be a by-product of hypopituitarism,[29] hypoadrenocorticism,[27, 28] and/or hypothyroidism[39] possibly supervening with chronic DCA administration. Further studies are needed to clarify this problem of the precise mechanism of the DCA-intensifying effect on cholesterol-induced atherosclerosis of chicks.

Obviously, our experiments by no means represent exhaustive studies on anterior pituitary-adrenal cortical factors and atherogenesis. Many other aspects of the relationship of this hormonal system to cholesterol metabolism and atherogenesis merit exploration. The need for such investigations is emphasized by data demonstrating the active role of the adrenal cortexes in sterol metabolism: their high content of cholesterol,[1, 9] their ability readily to discharge cholesterol,[40] to synthesize cholesterol,[41] and to accumulate ingested cholesterol.[1, 9, 42–44] Further, recent clinical studies[3] highlight the need to explore the effects of adrenal glycocorticoids (e.g. cortisone) on lipid metabolism and atherogenesis. Such studies are currently in progress in this laboratory.

* Bruger and Lowenstein also recorded negative results in studies on the effects of DCA on cholesterol-induced atherosclerosis of rabbits.[33]

Summary

The exhibition of desoxycorticosterone acetate over periods up to 15 weeks induces cardiac hypertrophy, polydypsia, adrenal hypoplasia, decreased comb size indexes and moderate nephrosclerosis in cockerels. A definite, but not severe, rise in blood pressure occurs. The polydypsia and hyperpiesis induced by DCA are increased by addition of 1 per cent sodium chloride to the mash; neither supervene in DCA-treated chicks on a low sodium diet.

The exhibition of DCA fails to influence cholesterolemia grossly in chicks on mashes with or without a cholesterol supplement. Correspondingly, gross atherogenesis is not significantly influenced by DCA in birds fed only plain mash. However, in cockerels given a mildly atherogenic supplement of cholesterol in their mash (0.25 per cent cholesterol), concomitant DCA exhibition increases the incidence and severity of atherosclerosis. Possible mechanisms of this DCA effect on cholesterol-induced atherogenesis are discussed.

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Water and Electrolyte Metabolism in Congestive Heart Failure

By GEORGE E. MILLER, M.D.

The over-all metabolic balance of sodium, chloride and water has been studied in 8 subjects recovering from congestive heart failure. During the release of edema the observed loss of water in excess of sodium and chloride, as they are normally present in extracellular fluid, has suggested that the concept of initial retention of sodium in the development of heart failure may be untenable.

SINCE 1944 when Warren and Stead[1] first attributed the fluid retention of chronic congestive heart failure to a specific renal dysfunction, an ever increasing interest has centered upon the kidney in an attempt to elucidate its part in the production of edema. Seven years later, although there has been no general agreement on the mechanism, it is believed by many workers that in heart failure there is an initial retention of sodium as a result of decreased glomerular filtration or increased tubular reabsorption of this ion or both, with a subsequent retention of water that results in increased extracellular fluid volume and pitting edema.[1-9]

According to current concepts the fluid retaining effect of sodium depends upon its position as the principal component of osmotically active base in the extracellular fluid compartment. Alterations in sodium content are reflected by retention or release of water if osmotic constancy (constant concentration of the sodium ion) is maintained. Retention of potassium, calcium, or magnesium does not lead to fluid retention since the physiologic concentration and range of these ions is so small that each contributes a negligible fraction to osmotic activity of this body fluid compartment. Having accepted sodium as the keystone in the development of edema it follows that the extracellular fluid concentration of this ion should be elevated, or at least in the high normal range, during a period of fluid retention.[10]

Present understanding of the relationship between extracellular and intracellular fluid would lead us to believe that there exists an osmotic equilibrium between these two compartments, and that this equilibrium is maintained principally by the free movement of water and a limited movement of univalent base across the cell membrane. (Whether alteration in intracellular binding of base by protein also contributes to the maintenance of this equilibrium is not known.) In the presence of sodium retention water might be expected to move from the intracellular to the extracellular space in response to the elevation of osmotic pressure in the latter compartment. In this situation the increase in extracellular fluid volume would be greater than the degree of weight gain (that is, fluid retention) would suggest.

The measurement of alterations in the volume and electrolyte composition of the major body fluid compartments during the development of congestive failure would be the most satisfactory approach to an investigation of this concept of edema formation. The hazard involved in this method seems too great to justify its use at this time. It does not, however, seem unreasonable to assume that the over-all metabolic changes which occur during recovery from heart failure are the opposite of changes which occur during the development of this syndrome. On the basis of this assumption observations might be made during recovery which would be useful in indicating the pathogenesis of this disorder.

It was upon this premise that the investigation reported here was undertaken. An analysis

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of the data has suggested to us that water, rather than sodium, is initially retained in cardiac decompensation with edema formation.

Materials and Methods

Subjects. The sera of 26 unselected patients with the usual manifestations of chronic congestive heart failure were obtained for electrolyte analyses. Of these patients 7 were selected for detailed metabolic balance study. This selection was made only on the basis of the ability and willingness of the patient to cooperate in such a study. These 7 included 2 (R. H. and J. W.) with arteriosclerotic cardiovascular disease, 2 (N. T. and L. M.) with cor pulmonale, 2 (M. O. and A. K.) with hypertensive cardiovascular disease, and one (E. S., who was studied during two episodes of heart failure) with rheumatic heart disease. Most of these patients had received digitalis and mercurial diuretics in the past. Despite such therapy the congestive failure had progressed in every instance and each was essentially at the peak of his break in compensation at the time of admission.

Methods. Metabolic balance studies of sodium and chloride were carried out on the Metabolism Ward of the Buffalo General Hospital. Because of the changing clinical condition of the subjects it was impossible to maintain a constant dietary intake of these substances. For this reason analysis of diets of individual patients seemed impractical and the dietary intake has been calculated from the tables of Reifenstein and associates.[11] Sample diets were prepared specifically for analysis, however, with the following results: in fourteen diet analyses the sodium content averaged 87.8 per cent of the calculated amount, while in three analyses the chloride content averaged 91.3 per cent of the calculated value. These discrepancies have been taken into consideration in the discussion of results and the conclusions that have been drawn.

Fluid was allowed freely during the period of observation.

Treatment, in every instance, consisted of bed rest and digitalis. In those patients who did not respond to this therapy in a satisfactory manner a mercurial diuretic was used as recorded. Saline cathartics (Phospho-Soda Fleet and effervescent sodium phosphate) were used in 6 subjects as recorded. The mineral content of these salts was determined by analysis and is included in the balance data.

Metabolic periods were three days in length. A thiocyanate space study was carried out on the first metabolic day in each instance. Fasting weight was determined each morning. A fasting blood specimen was collected on the first morning of each metabolic period and the serum stored at 10 C. until all chemical procedures had been carried out. A suitable aliquot of each 24 hour urine specimen was analyzed for sodium and chloride. Three day collections of feces were pooled and homogenized. An aliquot of this homogenate was dried, ashed and an acid solution of this ash used for the determination of sodium and chloride.

Sodium determinations were carried out on a Model 52 A Perkin-Elmer flame photometer using an internal lithium standard. Chloride was determined by the electrimetric titration method of Dean and Hawley.[12] Thiocyanate method was that of Elkinton and Taffel.[13]

Calculations. Alteration in body weight has been used as a measure of change in total body water content. Alteration in the volume of extracellular fluid was measured at the end of each metabolic period by a determination of the chloride space from the chloride balance and the serum chloride concentration. The initial extracellular fluid volume, from which subsequent calculations were derived, was measured by the dilution of sodium thiocyanate. It is recognized that the thiocyanate space is not an accurate measure of the extracellular fluid volume, but since it was the *change* in that volume rather than its absolute size which was of interest this inaccuracy may be disregarded. Such change might have been measured as adequately had the assumption been made that the extracellular fluid volume was initially represented, in the edematous patient, by 30 per cent of the body weight. Neither is there complete agreement that the chloride space is an accurate measure of the extracellular fluid compartment size. While it probably does measure this compartment in muscle there is evidence that in certain other tissues, notably the central nervous system, the gastric mucosa, the testes, there is a measurable portion of chloride in the intracellular space.[14, 17] This does not invalidate its use as an index of extracellular fluid volume.

Table 1.—*Serum Sodium Concentration in Congestive Heart Failure*

Investigator	No. of Patients	Mean Serum Sodium mEq./L.
Futcher and and Schroeder[18]	3	136.3
Mokotoff and co-workers[2]	16	135.3
Briggs and co-workers[3]	14	140.9
Fox[19]	27	(Significantly low)
Miller	26	135.2
Miller	54 (normals)	139.5

Observations

Serum Sodium. In the 26 patients included in this report the mean serum sodium level of

TABLE 2.—*Detailed Observations of Eight Subjects Recovering from Congestive Heart Failure.*

Patient	Metabolic Period	Weight	Drug	Sodium				Chloride				Comment
				Serum Conc.	Intake	Output	Balance	Serum Conc.	Intake	Output	Balance	
		Kg.		*mEq./L.*	*mEq.*	*mEq.*	*mEq.*	*mEq./L.*	*mEq.*	*mEq.*	*mEq.*	
R. H.	0	71.80		132.0				92.6				NaSCN space
	1	72.80	*	130.5	37.6	33.2	4.4	90.5	151.4	67.5	83.9	20.8 L.
	2		X	131.0	121.9	10.8	111.1	94.5	243.7	30.1	213.6	NH_4Cl 4.0
	3			132.5	53.2	9.6	43.6	105.5	209.7	60.7	149.0	Gm./day
	4	67.25	*	140.0	195.4	278.6	−83.2	105.8	415.3	571.3	−156.0	Metabolic p-
	5	69.30		130.0	29.9	3.7	26.2	102.7	255.3	54.8	200.5	riods 2
	6	64.45	**	139.5	37.2	328.2	−291.0	91.8	277.7	698.0	−420.3	through 10
	7	64.35	*	139.5	42.3	43.1	−0.8	99.0	270.3	162.9	107.4	
	8	63.95	*	137.0	174.2	152.2	22.0	102.9	400.3	362.7	37.6	
	9	63.08	X*	144.0	106.8	119.0	−12.2	110.2	266.8	275.9	−9.1	
	10	63.80		130.5	42.6	7.6	35.0	101.5	270.6	50.7	219.9	
	11	62.35	*	135.5	32.6	107.9	−75.3	101.2	30.9	324.7	−293.8	
					873.7	1093.9	−220.3		2792.0	2659.3	132.7	
N. T.	0	55.91		143.5				93.6				NaSCN space
	1	54.21		144.5	124.9	337.9	−213.0	100.8	110.4	359.1	−248.7	23.39 L.
	2	53.98		144.5	107.8	119.3	−11.2	90.5	83.1	120.8	−37.7	
	3	52.95	X*	135.5	175.6	251.9	−76.3	98.8	96.4	209.8	−113.4	
	4	53.45	X	144.5	173.2	72.3	100.9	89.2	92.0	28.5	63.5	
	5	53.85		145.5	134.6	94.9	39.7	95.6	117.5	63.8	53.7	
					716.1	876.0	−159.9		499.4	782.0	−282.6	
E. S.	0	71.56		125.5				93.2				NaSCN space
	1	67.20		145.0	86.6	642.8	−556.2	103.7	67.7	510.2	−442.5	22.70 L.
	2	66.75		141.0	96.0	92.8	3.2	99.5	74.9	64.5	10.4	
	3	66.60		140.0	96.0	46.1	49.9	101.8	74.9	70.8	4.1	
	4	66.00		141.5	95.0	62.0	33.0	98.6	73.8	65.2	8.6	
	5	66.60	X	140.5	163.5	76.9	86.6	93.3	74.8	35.4	39.4	
	6	66.65	X	137.5	163.0	74.7	88.3	108.7	72.7	43.2	29.5	
					700.1	995.3	−295.2		438.8	789.3	−350.5	
E. S. (2)	0	76.15		141.0				96.8				NaSCN space
	1	76.50		126.0	51.5	7.4	44.1	89.2	51.7	38.5	13.2	30.59 L.
	2	69.25	**	141.5	64.8	541.4	−476.6	92.8	59.2	678.9	−619.7	
	3	68.90	*	134.5	80.5	147.2	−66.7	88.3	72.7	39.4	33.3	
	4	67.40	*	134.0	82.5	197.9	−115.4	94.0	74.8	89.9	−15.1	
	5	64.70	*	135.5	82.2	436.0	−353.8	100.5	76.0	313.1	−237.1	
	6	62.71	*	133.0	91.5	266.8	−175.3	95.3	81.2	222.5	−141.3	
	7	62.31	*	137.5	91.5	74.5	17.0	94.2	81.2	112.7	−31.5	
					544.5	1671.2	−1126.7		496.8	1495.0	−998.2	
L. M.	0	70.86		143.5				92.4				NaSCN space
	1	70.45		139.5	64.2	103.1	−38.9	96.8	60.5	109.2	−48.7	24.69 L.
	2	65.95		136.0	89.9	603.0	−513.1	94.7	87.1	519.6	−432.5	
	3	64.05	#	137.5	180.9	442.9	−262.0	96.3	84.9	258.5	−173.6	
	4	63.83	#	138.0	154.1	153.7	0.4	94.3	63.3	84.7	−21.4	
	5	61.70	*	136.5	78.7	300.9	−222.2	87.2	72.7	282.5	−209.8	
	6	61.10	*	136.0	97.8	147.7	−49.9	88.9	99.9	126.4	−26.5	
					665.6	1751.3	−1085.7		468.4	1380.9	−912.5	

TABLE 2—*Continued*

Patient	Metabolic Period	Weight	Drug	Sodium				Chloride				Comment
				Serum Conc.	Intake	Outpu	Balance	Serum Conc.	Intake	Output	Balance	
		Kg.		*mEq./L.*	*mEq.*	*mEq.*	*mEq.*	*mEq.*	*mEq.*	*mEq.*	*mEq.*	
J. W.	0	86.70		141.0				101.0				NaSCN space
	1	84.85		143.0	71.7	180.8	−109.1	99.1	51.2	181.1	−129.9	18.60 L.
	2	84.51	X	141.5	124.3	71.4	52.9	92.4	41.9	26.3	15.6	
	3	82.10	X	132.5	90.4	109.3	−18.9	96.8	13.1	37.8	−24.7	
	4	81.65		140.5				88.5				
					286.4	361.5	−75.1		106.2	252.5	−139.0	
M. O.	0	45.35		137.5				99.6				NaSCN space
	1	40.32		132.6	48.3	682.7	−634.4	91.9				21.64 L.
	2	36.85	⁂	132.4	158.6	399.4	−240.8	94.2	57.2	342.0	−284.8	
	3	35.83	⁂	133.0	181.5	312.1	−130.6	91.1	59.1	191.7	−132.6	
	4	35.20		132.0	66.4	117.8	−51.4	92.1	58.0	133.2	−75.2	
	5	35.50		138.5	67.9	36.6	31.3	91.3	59.1	55.8	3.3	
					522.7	1550.6	−1025.9		233.4	727.7	−489.3	
A. K.	0	78.50		139.0				104.5				NaSCN space
	1	76.00	*	139.5	82.4	294.4	−212.0	94.7	57.4	360.3	−302.9	
	2	71.75	*	139.5	59.9	352.1	−292.2	102.4	44.1	375.4	−331.3	33.98 L.
	3	70.55	*	140.5	50.1	185.3	−135.2	102.9	38.3	202.8	−164.5	
	4	68.90	*	137.5	51.4	162.3	−110.9	103.5	37.5	131.0	−93.5	
	5	67.15	*	132.0	52.7	207.3	−154.6	97.5	52.7	149.1	−96.4	
					296.5	1201.4	−904.9		230.0	1218.6	−988.6	

* represents single 2 cc. dose of Mercuhydrin, intravenously administered.
** indicates two 2 cc. doses during one metabolic period.
X represents 15 cc. Phospho-Soda (Fleet).
⁂ represents a purgative dose, effervescent sodium phosphate.

135.2 mEq. per liter is distinctly lower than the mean value of 139.5 mEq. per liter for 54 normal individuals (table 1). Although data in the literature are meager on this point, the available reports have been included in table 1.

Sodium Balance. In each of the 8 subjects studied in detail (table 2) the clinical recovery from congestive heart failure was accompanied by a loss of the pitting edema which was measured by the change in body weight. In figure 1 this loss of weight has been plotted against the over-all sodium balance. If 1 Kg. of weight loss represents 1 liter of extracellular fluid water, then each Kg. of weight loss should be accompanied by a loss of 150 mEq. of sodium, the amount of sodium in this quantity of normal extracellular water. This normal relationship is indicated by the diagonal line. In no instance did this normal relationship exist. Each of the 8 subjects lost significantly more water than could be accounted for by

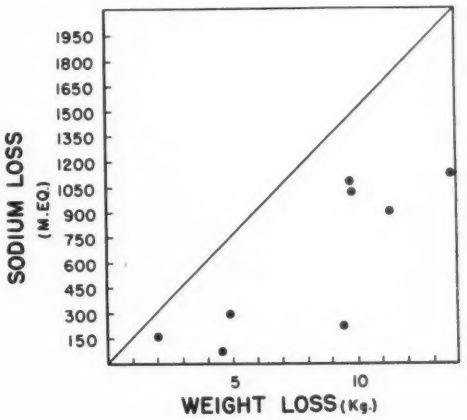

FIG. 1. See text.

the sodium balance. In terms of this ion the edema fluid lost was a solution whose osmotic pressure was lower than normal.

Fluid Compartment Volume Changes. An analysis of the chloride balance data (table 2) indicates that with the exception of N. T., the total edema fluid lost by each subject contained less chloride than would have been present had that fluid been extracellular fluid of normal composition. Over-all chloride balance alone, however, is inadequate to determine alteration in the extracellular fluid volume. A calculation of the chloride space (table 3) reveals that in 4 patients (R. H., E. S. (2), J. W. and A. K.) the total fluid lost during recovery from heart failure far exceeded the loss of extracellular fluid volume while in two instances (E. S. and L. M.) it was slightly in excess of the extracellular fluid loss. (The data on M. O. are incomplete: during the period of greatest weight loss the chloride balance was not determined.)

TABLE 3.—*Comparison of Alteration in Total Body Water and Extracellular Fluid Volume during Recovery From Cardiac Failure*

Subject	Change in Body Weight	Change in Chloride Space
	Kg.	*Liters*
R. H.	−9.45	−0.45
N. T.	−2.06	−3.45
E. S.	−4.91	−4.63
L. M.	−9.76	−9.30
E. S. (2)	−13.84	−9.75
J. W.	−4.60	−0.63
A. K.	−11.35	−7.70

A reduction in total body water that is greater than the loss of extracellular water suggests that the difference between these two quantities is provided by a loss of intracellular water. Such a movement of water out of cells during recovery from heart failure would seem to indicate the passage of water into cells at some time during the development of this syndrome.

In one subject (N. T.) the loss of extracellular fluid was greater than the loss of body water. The one other subject with cor pulmonale fell in that group in which the body water loss was only slightly greater than the extracellular fluid loss. In these 2 patients alone was there an initial elevation of the serum sodium concentration above the normal mean value. In patient N. T. a respiratory acidosis was demonstrated; in L. M. it was presumed to be present. It is conceivable that the metabolic pattern of congestive heart failure associated with cor pulmonale may be influenced by an earlier alteration in the acid-base balance produced by the primary pulmonary disease, and that the data on such patients are not comparable to that on other types of cardiac edema.

Discussion

The significance of the finding of reduced concentration of sodium in the serum of patients in congestive heart failure might be questioned since the range of this value in normal individuals may be fairly wide. Two of the three other groups whose data revealed a similar reduction of serum sodium did not comment upon this finding. This may indicate that the reported levels were normal in their respective laboratories. It seems more likely that this reduction was considered insignificant. Yet it is arresting that in four laboratories the extracellular concentration of sodium in this condition should be at the lower reach of the normal range, rather than at its upper extremity, where it might be expected in the patient with edema resulting from initial sodium retention.

In none of the subjects reported here was the loss of 1 Kg. of body water accompanied by the loss of 150 mEq. of sodium. From Newman's[4] metabolic balance charts of 2 patients recovering from heart failure, it is evident that a similar loss of water in excess of sodium was present. The direct observation of a lowered osmotic pressure in the extracellular fluid is thus supported by this derivation from the data on water and sodium excretion.

The movement of water out of cells during the recovery from heart failure has also been suggested by Schroeder.[20] In 17 of 39 patients he pointed out that the excretion of chloride was less than would have been present had the weight loss reflected an excretion of extracellular accumulation of edema fluid. Although

the data of Seymour and co-workers[21] are not entirely comparable to those reported here since their measure of extracellular fluid volume was the thiocyanate space, it is interesting to note their finding of a reduction of extracellular fluid volume that was smaller than the reduction of body weight in 3 of 6 patients recovering from heart failure. This again suggests the accumulation of intracellular as well as extracellular fluid during the development of cardiac edema.

The universally recognized fluid retaining effect of excessive amounts of sodium, as well as the spectacular success of sodium restriction in the treatment of edema, has focused investigative attention upon this ion, often at the expense of other factors which might be operative in the production of edema. However, certain observations have been made in edematous states which suggest some fundamental alteration in water metabolism that is unrelated to the disordered electrolyte state. Among these findings are the delayed water diuresis in cardiac, hepatic and nephrotic edema. There is suggestive evidence that the alteration in renal functions in congestive heart failure includes not only disordered sodium filtration and reabsorption, but also an independent fault in the handling of water.[5] Recently an antidiuretic material has been demonstrated in the urine of patients with cardiac edema[22] as it has previously been shown in those with fluid retention and cirrhosis,[23,24] nephrotic syndrome,[25] and acute glomerular nephritis.[25]

The metabolic adjustments that follow the retention of water would be essentially the converse of those following the retention of sodium.[26] An initial reduction of the extracellular osmotic pressure, represented by a lowering of the serum sodium concentration, might constitute a stimulant to adrenal cortical activity[27] with a resultant retention of sodium. Extracellular hypotonicity would be reflected by a similar change in the intracellular fluid which might be most promptly accomplished by the movement of water into cells. Under these circumstances the increase in total body water (measured by weight gain) would be greater than the increase in volume of the extracellular fluid compartment. During recovery from edema which had developed in this manner the opposite events would be expected to occur: sodium loss would be less than the amount present in a volume of extracellular fluid represented by the weight loss; the reduction in extracellular fluid volume would be smaller than the reduction in body weight. The observations made in the 8 patients reported here are compatible with this pattern and suggest that the edema of congestive heart failure may be the result of an initial retention of water rather than an initial retention of sodium.

This conclusion should in no way be interpreted as a denial of the importance of sodium restriction in the treatment of edematous states, nor of the role of this ion in contributing to the development of edema. Neither should it imply any value to the restriction of water in congestive heart failure. The measurements that have been made in this investigation are of over-all metabolic changes, not discrete measurements of the moment to moment pathogenic changes. There are certain reasonable speculations that might be made to resolve this seeming paradox, but it would be more proper to withhold such speculation until it can be supported by accumulated evidence.

In a study in which conclusions of a physiologic rather than a pharmacologic nature are drawn, therapeutic administration of drugs in these experimental subjects might be the object of legitimate criticism. However, from the presentation of the observations and derived data it would seem clear that there was no essential difference in the over-all metabolic changes of those patients who received mercurial diuretics and those who did not. It should be kept in mind that the composition of the edema fluid which provides the substance of the diuresis is not altered by the diuretic agent. The administration of a saline cathartic did not change in any significant way the course of congestive failure in these patients.

Although the data presented here have suggested that the edema of heart failure is initiated by water retention rather than sodium retention, the mechanism of such a metabolic abnormality is obscure. The presence of an antidiuretic material in the urine of patients

with several types of edema may suggest the participation of the posterior pituitary either directly or indirectly in these edematous states, but the identity of this material, or materials, has not been established. It is entirely possible that other sources of such hormonal substances have yet to be discovered, or that other mechanisms may be involved.

Summary and Conclusions

1. Metabolic balance studies of sodium and chloride were carried out in 8 subjects recovering from congestive heart failure. The over-all metabolic changes during recovery were assumed to be the opposite of changes during development of cardiac edema.

2. Recovery from heart failure was accompanied by loss of body weight (fluid); by a loss of sodium that was less than the weight loss demanded if that weight loss were due to a release of extracellular fluid; and by a reduction of extracellular fluid volume smaller than the reduction in body weight.

3. These findings do not fit the pattern anticipated in the loss of edema resulting from initial sodium retention; they do fit the pattern anticipated in the loss of edema resulting from initial water retention.

4. The observations suggest that the edema of congestive heart failure results from an initial retention of water rather than sodium.

5. No therapeutic implications are drawn.

Acknowledgment

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Interrelationships of Cardiac Output, Blood Pressure, and Peripheral Resistance during Normal Respiration in Normotensive and Hypertensive Individuals

By ARNOLD H. WILLIAMS, M.D., AND ARTHUR L. GROPPER, M.D.

The effects of normal respiration upon the heart, blood pressure, and peripheral circulation were studied in normotensive and hypertensive subjects. Changes of right and left ventricular output were measured by the ballistocardiogram and the pressure-pulse method of Remington, peripheral blood flow by plethysmographs. The central and peripheral changes were interrelated and evidence is presented that the latter are chiefly due to the effects of intrathoracic pressure upon cardiac filling.

FOR MANY years it has been known that quiet respiration is accompanied by certain changes in the dynamics of the circulation. On inspiration the output of the right ventricle increases, that of the left decreases,[1-6] arterial pressure falls[7-11] and regional blood flow is diminished.[12-14] During expiration the direction of the changes is reversed. Their origin has been attributed to the effects of variations of intrathoracic pressure upon the filling of the right heart which in turn affects the filling of the left heart.[2-6] The depth, type and rate of respiration[7, 11] influence the magnitude of the changes to some degree. There is no information on the effects of quiet respiration upon peripheral resistance.

Most of the above studies have been made on laboratory animals. Rather drastic procedures were used and either central or peripheral circulatory changes were investigated. The present study represents an attempt to interrelate all the changes in man, using technics designed to cause as little disturbance to the subject as possible. In addition, the reactions of normotensive and hypertensive individuals were compared.

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METHODS

Simultaneous measurements were made of the variations of the output of each ventricle, of arterial pressure and of volume flow through various peripheral areas. Blood pressure was measured directly by a Hamilton optical manometer[15] through a 20 gage hypodermic needle in the brachial artery. Respiration was recorded by a pneumograph strapped about the thorax. Directional changes in regional blood flow were estimated with photoelectric plethysmographs applied usually to the lobe of the ear, the toe tip and finger tip. In a few instances they were followed in the forearm and hand with an air plethysmograph. Similar changes were found in other regions of the body, i.e., the scrotum, cheek, tongue, and rectovaginal septum. These instruments did not provide quantitative measurements of blood flow, but directional changes were estimated from the diastolic volume of the part. All electrical signals were led through direct current amplifiers into Sanborn galvanometers; recordings were made on a photokymograph run at a speed of 5 or 25 mm. per second. Inasmuch as the outputs of left and right ventricles vary in opposite directions during respiration, it was necessary to devise methods for separating these two functions. Total cardiac output from beat to beat was calculated from tracings taken on a high frequency ballistocardiograph of Wilkins' design.[16] The oscillations of the table were recorded by means of a photoelectric pressure recorder with a suitable rubber membrane. An attempt to estimate beat-to-beat variations of left ventricular stroke volume utilizing the K wave of the ballistocardiogram was unsuccessful. In this study the percentile changes of left ventricular output from inspiration to expiration were estimated using the pressure-pulse method of Remington.[19] Estimates of the percentile changes of right ventricular

TABLE 1.—*Circulatory Changes during Quiet Respiration*

Name, Sex and Age	Diagnosis	Condition of Patient during Expt.	Surface Area (Sq. M.)	Resp. rate (per min.)	Pulse Rate (per min.)			Blood Pressure (mm. Hg)			Left Ventricular Stroke Index† (cc. per beat)			Ballistocardiographic Stroke Index (cc. per beat)				Peripheral Resistance‡			Type of Ballistocardiogram§
					Insp.	Exp.	Exp. % Change	Insp.	Exp.	% Change	Insp.	Exp.	Exp. % Change	Insp.	Exp.	Insp. % Change	Mean	Insp.	Exp.	Exp. % Change	
R. I. M, 13	Alcoholism	calm	1.82	20	79.8	73.2	−8.3	115.0 56.0	119.0 57.0	+3.5 +1.8	57.4	60.3	+5.1	29.9	25.7	+16.3	28.3	2.89	2.81	−2.8	N
R. S. M, 16	Pneumonia, Convalescent	agitated	1.71	34	47.5	45.9	−3.5	139.5 60.8	141.5 62.7	+1.4 +3.1	71.9	71.4	−0.7	36.3	32.0	+13.4	33.6	2.74	2.81	+2.6	M_1
O. H. M, 40	Malnutrition	calm	1.67	26	85.1	81.9	−3.9	114.0 58.7	118.9 61.8	+4.3 +5.3	53.4	55.1	+3.2	57.7	42.1	+37.1	53.1	1.55	1.57	+1.3	M_1
L. M. M, 22	Pneumonia, Convalescent	tense	1.65	21	56.8	54.3	−4.6	121.3 58.2	125.2 60.2	+3.2 +3.4	61.0	62.0	+1.6	53.7	37.7	+42.4	45.3	1.86	1.89	+1.6	N
B. M. M, 24	Tonsilitis, Convalescent	calm	1.58	21	60.6	58.5	−3.6	109.6 54.5	112.5 55.5	+2.7 +1.8	53.7	55.5	+3.4	58.2	54.0	+7.8	55.5	1.4	1.38	−1.4	N
T. B. M, 47	Indolent Ulcer	calm	1.87	20*	75.0	71.0	−5.6	126.4 59.5	127.9 60.6	+1.2 +1.9	63.5	63.7	+0.3	56.8	51.8	+9.7	54.6	1.58	1.6	+1.3	N
T. C. M, 35	Alcoholism	tense	1.77	21	76.0	71.0	−7.04	103.5 64.5	106.1 65.6	+2.5 +1.7	37.7	38.9	+3.2	45.3	32.5	+39.4	39.4	2.06	2.04	−1.0	N
J. V. M, 20	Reiter's Syndrome	tense	1.73	24	76.9	73.8	−4.0	105.4 67.6	109.6 69.2	+4.0 +2.4	36.3	38.4	+5.8	39.6	32.8	+20.8	35.8	2.38	2.31	−2.9	N
R. F. M, 24	Duodenal Ulcer	tense	1.87	21	75.6	68.0	−10.1	126.4 59.4	132.5 60.6	+4.8 +2.0	64.8	67.2	+3.7	49.2	39.5	+24.6	44.5	1.98	1.97	−0.5	N
M. B. M, 64	Pneumonitis, Convalescent	calm	1.58	24*	102.0	98.4	−3.7	133.0 75.0	139.5 75.8	+4.9 +1.1	53.1	56.9	+7.2	37.0	47.5	−22.1	44.0	2.32	2.22	−4.31	N (M_2 on Insp.)
S. S. M, 44	Alcoholism	calm	1.83	14	71.4	68.3	−4.5	140.6 79.8	146.5 82.7	+4.2 +3.6	53.6	55.1	+2.8	44.5	35.0	+27.1	40.8	2.58	2.62	+1.6	N
Mean..... 33.5			1.73	22.4	73.3	69.5	−5.3	121.3 63.1	125.4 64.7	+3.3 +2.6	55.1	56.8	+3.2	46.2	39.1	+19.7	43.2	2.12	2.11	−0.41	
C. F. M, 49	Essential Hypertension	tense	1.99	16	52.1	50.4	−3.4	224.0 101.0	232.0 103.0	+3.6 +2.0	74.3	74.9	+0.8	47.0	37.9	+24.0	43.1	3.5	3.58	+2.3	N (L on Insp.
Ibid M, 49	Essential Hypertension	anxious	1.99	21*	59.0	58.0	−1.7	197.0 90.0	202.0 90.0	+2.5 +0.0	74.1	77.7	+4.9	42.2	36.4	+16.5	39.3	3.47	3.35	−3.5	N (L on Insp.)
P. P. F, 53	Essential Hypertension	anxious	1.63	24	104.3	101.6	−2.4	172.3 88.6	175.1 89.1	+1.6 +0.56	65.7	66.9	+1.8	34.4	24.3	+41.6	29.8	4.14	4.10	−1.0	L
P. W. M, 36	Essential Hypertension	calm	1.87	18	76.4	74.1	−3.0	188.0 108.0	195.5 108.3	+4.0 +0.28	54.2	56.2	+3.7	38.0	25.4	+49.7	32.9	4.33	4.28	−1.2	N
M. L. M, 22	Essential Hypertension	tense	2.05	32	93.0	90.0	−3.3	155.0 90.5	161.5 93.8	+4.2 +3.6	53.5	54.1	+1.1	20.4	14.0	+45.7	17.7	6.61	6.79	+2.7	N (some L)

Table concluded on following page

TABLE 1—*Continued*

Name, Sex and Age	Diagnosis	Condition of Patient during Expt.	Surface Area (Sq. M.)	Resp. rate (per min.)	Pulse Rate (per min.)			Blood Pressure (mm. Hg)			Left Ventricular Stroke Index† (cc. per beat)			Ballistocardiographic Stroke Index (cc. per beat)				Peripheral Resistance‡			Type of Ballistocardiogram§
					Insp.	Exp.	Exp. % Change	Insp.	Exp.	% Change	Insp.	Exp.	Exp. % Change	Insp.	Exp.	Insp. % Change	Mean	Insp.	Exp.	Exp. % Change	
L. F. M, 24	Essential Hypertension	agitated	1.42	18	99.4	95.9	−3.7	217.3/119.7	228.3/123.8	+5.1/+3.4	54.4	54.5	+0.2	34.4	28.1	+22.4	30.7	5.17	5.39	+4.3	M_1
C. S. M, 50	Essential Hypertension	calm	1.88	15	80.4	71.5	−12.5	211.5/106.5	237.0/113.0	+12.0/+6.1	65.2	67.1	+2.9	36.3	22.4	+62.0	29.9	5.04	5.36	+6.35	N
A. S. M, 30	Essential Hypertension	calm	1.90	28	97.2	94.8	−2.53	170.3/89.6	174.8/91.4	+2.6/+2.0	63.6	64.5	+1.4	40.1	28.1	+42.7	34.7	3.54	3.57	+0.85	N
Ibid M, 30	Essential Hypertension	calm	1.89	22	75.7	73.4	−3.0	180.2/103.9	189.0/106.6	+4.9/+2.5	55.6	55.8	+0.4	47.2	32.2	+46.6	39.6	3.4	3.52	+3.5	N
N. J. M, 22	Glomerulonephritis, Hypertension	calm	1.99	24	86.5	83.7	−3.1	149.0/78.7	152.9/80.7	+2.6/+2.5	60.6	61.3	+1.2	32.4	27.2	+19.1	29.3	3.38	3.72	+1.0	M_1
W. B. M, 56	Malignant hypertension, Uremia	calm	1.89	13*	95.5	95.5	0.0	200.8/100.0	214.5/102.0	+6.8/+2.0	67.0	70.3	+4.9	56.5	39.2	+44.1	49.5	2.91	2.89	−0.7	M_1
Mean 38.3			1.86	21.0	83.6	80.8	−3.5	187.8/97.9	196.6/100.2	+4.5/+2.3	62.6	63.9	+2.1	39.0	28.7	+37.7	34.2	4.14	4.23	+1.3	
F. T. M, 67	Arteriosclerotic hypertension	calm	1.83	27	75.3	74.0	−1.7	239.2/94.0	241.9/96.0	+1.1/+2.1	85.8	81.6	−1.4	55.5	32.8	+69.2	45.8	3.3	3.4	+3.0	M_2 (calculated as N)
E. H. F, 20	Coarctation of Aorta, 5 months pregnancy	tense	1.79	20*	88.2	80.6	−9.4	162.9/98.1	167.9/100.6	+3.1/+2.6	50.6	51.2	+1.2	31.6	26.3	+20.1	27.6	4.52	4.6	+1.8	N (no K wave)

Percentile changes are expressed in terms of inspiratory values except for the BCG values, which are expressed in terms of expiratory values.

* Respiration irregular

† Calculated by the pressure pulse of Remington and co-workers.[19]

‡ Formulas for calculation of resistance

$$\text{Resistance}_{\text{insp.}} = \frac{\text{Diastolic pressure} + [0.4 \times (\text{Systolic pressure}_{\text{insp.}} - \text{Diastolic pressure}_{\text{exp.}})]}{(\text{BCG stroke index}_{\text{mean}} - [0.5 \times \% \text{ change left ventricular stroke index} \times (\text{BCG stroke index}_{\text{mean}})]}$$

$$\text{Resistance}_{\text{exp.}} = \frac{\text{Diastolic pressure} + [0.4 \times (\text{Systolic pressure}_{\text{exp}} - \text{Diastolic pressure}_{\text{exp.}})]}{(\text{BCG stroke index}_{\text{mean}} + [0.5 \times \% \text{ change left ventricular stroke index} \times (\text{BCG stroke index}_{\text{mean}})]}$$

§ Type of BCG complex: N = normal, L = late downstroke, M_1 = late M, M_2 = double i or mid M.[20]

output (SV_R) were made by subtracting the changes of left ventricular output (SV_L), as obtained from the pressure-pulse method, from the total percentile changes recorded in the ballistocardiogram ($SV_R + SV_L$).*

* The respiratory variations of the ballistocardiograph reflect changes in the output of both ventricles. They vary in opposite directions during the respiratory cycle; their sum is recorded by the ballistocardiograph. The ballistocardiographic variations are largely due to changes in right ventricular output,[17,18] left ventricular output varying comparatively much less. The correct method for calculating right ventricular output (SV_R) is as follows:

$$\textit{Inspiration}\ SV_R = BCG_{mean} - \frac{\Delta SV_L + \Delta BCG}{2}$$

$$\textit{Expiration}\ SV_R = BCG_{mean} + \frac{\Delta SV_L - \Delta BCG}{2}$$

Patients were obtained from the clinic and wards of St. Louis City Hospital. Eleven were normoten-

sive, 11 suffered from "essential" hypertension of varying degrees of severity, and 2 had hypertension from other causes. The two groups were comparable in age and included 22 men and 2 women. The laboratory was air-conditioned at a constant temperature of 78 F., and all experiments were carried out in semidarkness. The only disturbing stimulus was the arterial puncture, done after periarterial novocaine infiltration. In most instances measurements were obtained during quiet relaxed breathing (table 1).

rated and averaged in all of the respiratory cycles of the strip. The ballistocardiographic changes were calculated according to the altitude formula of Starr and Schroeder.[20] Left ventricular output was estimated from the data of table 2 of Remington and co-workers,[19] the pressure-pulse values being obtained from the arterial pressure tracings. Peripheral resistance was calculated as the ratio of the mean arterial pressure to the mean ballistocardiographic stroke index, mean blood pressure being considered as diastolic pressure + 40 per cent of the

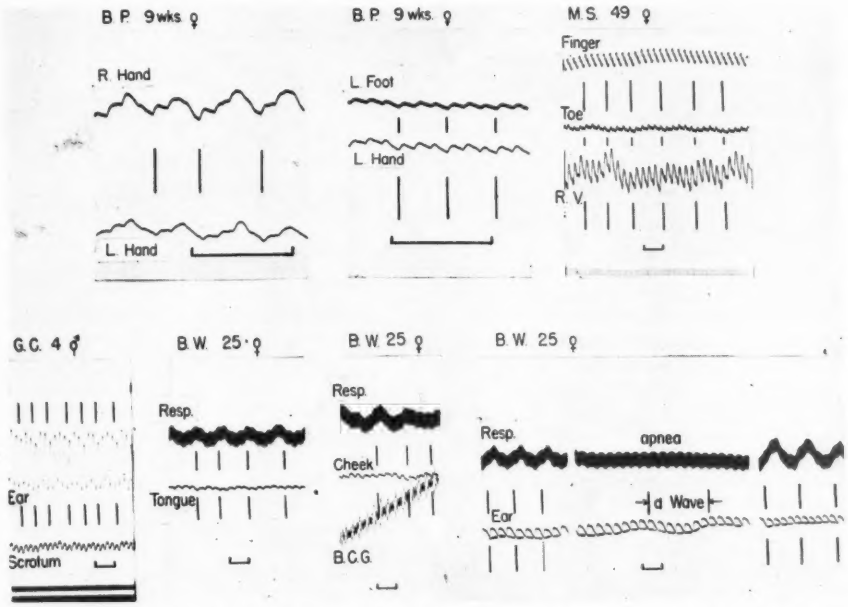

FIG. 1. Respiratory variations of peripheral blood flow. These plethysmographic records, selected from various patients, show that peripheral blood flow varies with respiration in all parts of the body, but stops during apnea although α waves continue (lower right). The vertical lines point to the decrease of blood flow during inspiration (up in the respiratory tracing). In all records the volume changes due to the pulse are superimposed on the slower respiratory changes. The bracket at the bottom of each record represents a time interval of two seconds. The label R.V. (upper right) indicates rectovaginal septum.

A representative 20 second section of each record was selected for analysis and beat-to-beat measurements were made of each function. The peak changes of blood pressure and both measures of cardiac output, during inspiration and expiration, were separated and averaged in all of the respiratory cycles of the strip. The ballistocardiographic changes were calculated according to the altitude formula of Starr and Schroeder.[20] Left ventricular output was estimated from the data of table 2 of Remington and co-workers,[19] the pressure-pulse values being obtained from the arterial pressure tracings. Peripheral resistance was calculated as the ratio of the mean arterial pressure to the mean ballistocardiographic stroke index, mean blood pressure being considered as diastolic pressure + 40 per cent of the pulse pressure (see footnote to table 1). Directional changes of volume of the extremities were estimated from diastolic values of the plethysmographic tracings.

where BCG_{mean} is average cardiac output throughout a respiratory cycle, ΔSV_L is the respiratory change in left ventricular stroke volume calculated by the pressure-pulse method,[19] and ΔBCG is the total respiratory change in the ballistocardiographic values. In actual practice, because of the discrepancy between the absolute values obtained by the two methods of determining cardiac output, only percentile changes were studied.

RESULTS

Respiratory variations of blood flow were found in every peripheral area in which measurements were made. They stopped during periods of apnea (fig. 1). The relationship of these changes to those of cardiac output and blood pressure can be seen in figure 2. When the beat-to-beat calculations were made of cardiac out-

put by the pressure-pulse and ballistocardiographic methods, it was found that the two changed in opposite directions.* Blood pressure, systolic more than diastolic, and peripheral blood flow mirrored the changes in left ventricular output. Changes in the volume of the forearm followed the level of blood pressure with a lag of approximately one beat (fig. 3). This interrelationship of central and peripheral changes was constant in all parts of the body studied.

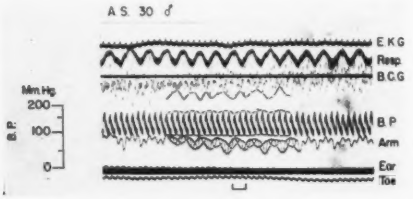

FIG. 2. The interrelationship of the central and peripheral circulatory changes during respiration. This record, taken at a slow camera speed, shows the interrelationships of circulatory changes during respiration in a 30 year old hypertensive male (A. S.). From top to bottom are the electrocardiogram (lead II), respiration (the peaks indicate inspiration), the ballistocardiogram (BCG), brachial blood pressure (with the scale in mm. of Hg at the left), volume of the forearm (down indicates an increase), volume of the pinna of the ear, and of the second toe (up indicates an increase). The variations have been underlined for accentuation in the central portion of the record. During inspiration the ballistocardiographic complexes increase in size, blood pressure falls, and the volume of the peripheral parts diminish. All these changes are in the opposite direction during expiration. The bracket at the bottom of the record indicates a two second interval.

The respiratory variations of blood pressure were often of considerable magnitude, systolic varying as much as 26 mm. Hg and diastolic, 6 mm. Hg. The ballistocardiographic stroke index changed by as much as 69 per cent, while the maximal change of the pressure-pulse index was only 7.2 per cent, the greatest individual variations being found in hypertensive patients (table 1). A comparison of the respiratory changes of right and left ventricular stroke output, as calculated by these methods, showed those of the right to be very much greater than those of the left in every individual but one (fig. 4). There was an apparent difference in the variation of left ventricular stroke volume between the normotensive and hypertensive

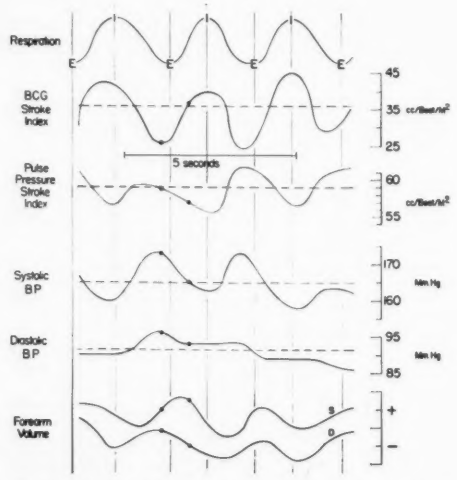

FIG. 3. Beat-to-beat relationships of central and peripheral circulatory changes during respiration. Three respiratory cycles of a hypertensive patient (A. S.) have been plotted. During the inspiratory phase, between the first two vertical lines, the ballistocardiographic (BCG) stroke index shows an increase of right ventricular stroke volume while the pressure-pulse stroke index shows a decrease of the output from the left side of the heart. The opposite changes occur during expiration (between the second and third vertical lines). The discrepancy between the magnitude of the two stroke indexes is explained in the text. The changes of systolic, and to a lesser extent diastolic, blood pressure parallel those of the output of the left heart as does the volume of the forearm (S and D indicate systolic and diastolic volume respectively). However, the latter shows a lag of one beat. The pulse rate varied between 73 and 75 per minute, the black dots showing individual beats.

groups. The calculated changes in right ventricular output were actually greater on the average in the hypertensive group.

An attempt was made to interrelate the magnitude of the changes of blood pressure and stroke index (obtained by both the ballistocardiographic and the pressure-pulse methods) but no correlation was found. Although variations

* In 2 patients left ventricular output decreased during expiration, and in one the output, calculated from the ballistocardiograph, decreased during inspiration (table 1).

were of minor degree, the calculated values for peripheral resistance might possibly be interpreted as compensatory (peripheral resistance decreasing during a rise of blood pressure) in 6 of the 11 normotensive individuals but in only 4 of the 13 hypertensives; however, only 6 showed changes greater than 3 per cent (table 1).

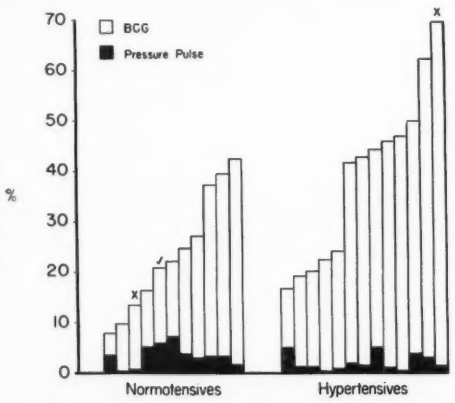

FIG. 4. Percentile respiratory changes of right and left ventricular stroke indexes. The black portion of each bar represents percentile changes of left ventricular stroke index (pressure-pulse method) while the total height of each bar represents the total percentile changes of the ballistocardiogram. The open portion of each bar, therefore, represents the changes of right ventricular stroke index (that portion of the ballistocardiographic change due to variations in the output of the right heart). In every case except the first normotensive it is considerably greater than that of the left heart. This variation is more pronounced in the hypertensive group. In the 2 cases marked with an *x*, left ventricular stroke volume increased during inspiration; in the patient marked with a check the ballistocardiogram showed a decrease during inspiration.

DISCUSSION

Validity of the Methods Used

The methods used for the estimation of right and left ventricular stroke volume are open to criticism but there are no others which provide beat-to-beat measurements of these functions. It is probable that they are adequate to indicate general trends for reasons to be brought out below, but they cannot be considered to be quantitative. Both are probably semiquantitative. The plethysmographs afford only indirect measurements of directional changes of blood flow as they merely measure alterations in the volume of the part and in the amplitude of the pulse.

The present paper is the first attempt to quantitate the respiratory variations of the output of the right heart by the ballistocardiogram. While the kinetic energy of the blood ejected by the left ventricle is thought to contribute a somewhat greater proportion to the forces which produce the ballistocardiographic complex, the respiratory variation of the complexes is believed to be largely a reflection of changes of right ventricular ejection.[17, 18] Although other factors are known to affect the respiratory variations, i.e., positive pressure breathing[21] which diminishes right ventricular output,[22] myocardial disease,[23] and pooling in the splanchnic bed,[24] they do not appear to be of significance in the present study. The values of respiratory changes of right ventricular stroke volume estimated by cardiac catheterization in man[5] are of the order of magnitude of those calculated above (table 1). The respiratory changes observed in the stroke volume of the left heart were small. The method used provides only an estimate of the alterations in that the calculations are based on arbitrary values of functions which are known to differ from individual to individual. Consequently, it might be inadequate for the quantitation of such small variations of stroke index. It is difficult to conceive, however, that the method could be so inaccurate as to be erroneous in regard to direction. It is striking that the calculated percentile changes of left ventricular stroke volume are also within the range estimated by cardiac catheterization in man.[5]

When the values of the mean ballistocardiographic stroke indexes were corrected so as to be comparable to those obtained with direct Fick methods, for example, $BCG_{mean} + 0.18\ BCG_{mean}$,[25] they gave a good correlation with the pressure-pulse stroke index in 9 of the 11 normotensive patients and in 9 of the 13 hypertensives, provided that errors up to 20 per cent were allowed in both methods.* The corre-

* These methods of estimating cardiac output have been found to give a good correlation, within 20 per cent, with direct Fick determinations.[19, 25]

lation was good without this correction in the normotensives (table 2). A correlation of this range is not insignificant in view of the indirect methods used.

On the other hand no correlation was found between the magnitude of the respiratory variations of blood pressure and those of left ventricular stroke index in each individual, as might be expected. The calculated change of peripheral resistance did not account for the difference. It is possible that the effects of intrathoracic pressure may have obscured the correlation.

TABLE 2.—*Correlation of Stroke Index by Ballistocardiographic and Pressure-Pulse Methods*

Patients	BCG*	BCG† + 0.18 BCG (A)	(A) +20%	(A) −20%	P.P.‡ (B)	(B) + 20%	(B) −20%	Correlation of 5 cc. or Less§
Normotensives								
R. J.	28.3	33.4	40.1	—	58.7	—	47.0	No
R. S.	33.6	39.7	47.6	—	71.7	—	57.4	No
O. H.	53.1	62.7	—	50.1	54.7	—	—	Yes
L. M.	45.3	53.5	64.1	—	61.2	—	—	Yes
B. M.	55.5	65.5	—	52.4	54.0	—	—	Yes
T. B.	54.6	64.4	—	—	63.6	—	—	Yes
T. C.	39.4	46.5	—	37.2	38.1	—	—	Yes
J. V.	35.8	42.3	—	33.8	38.2	—	—	Yes
R. F.	44.5	52.5	63.0	—	65.2	—	—	Yes
M. B.	44.0	51.9	—	—	55.0	—	—	Yes
S. S.	40.8	48.2	57.8	—	54.7	—	—	Yes
Hypertensives								
C. F.	43.1	50.9	61.0	—	73.6	—	58.9	Yes
C. F.	39.3	46.4	55.6	—	74.6	—	59.7	Yes
P. P.	29.8	35.2	42.2	—	66.1	—	52.9	No
P. W.	32.9	38.8	46.6	—	55.4	—	44.3	Yes
M. L.	17.7	20.9	25.1	—	53.7	—	43.0	No
L. F.	30.7	36.2	43.5	—	54.4	—	43.5	Yes
C. S.	29.9	35.3	42.3	—	66.5	—	53.2	No
A. S.	34.7	41.0	49.1	—	64.2	—	51.4	Yes
A. S.	39.6	46.7	56.1	—	55.7	—	—	Yes
N. J.	29.3	34.6	41.5	—	60.9	—	48.7	No
W. B.	49.5	58.4	70.1	—	69.0	—	—	Yes
F. T.	45.8	54.0	64.9	—	85.2	—	68.2	Yes
E. H.	27.6	32.6	39.1	—	50.6	—	40.5	Yes

* Ballistocardiographic stroke index.

† Ballistocardiogram corrected so as to be within the range of cardiac output determined by the Fick principle.[28]

‡ Pressure-pulse stroke index. This equals that obtained by the Fick principle within ± 20 per cent.[19]

§ Correlation within 5 cc. where errors up to 20 per cent are allowed in both methods (see text and references 19 and 25).

Theoretic Considerations

The mechanism of the various circulatory changes accompanying quiet breathing is not entirely understood. There are two major schools of thought.[26, 27]

1. The rate of filling of the right heart depends upon intrathoracic pressure, if systemic venous pressure is constant. During inspiration intrathoracic pressure falls and consequently venous return and filling are increased. Right ventricular output and pulmonary arterial pressure increase; the pulmonary vascular bed is enlarged more than enough to compensate for the increased stroke volume, and therefore blood pools in the lungs as a result of these events. Filling of the left heart is reduced, its output diminished, and blood pressure falls. All these changes are reversed during expiration. The pulmonary vascular bed therefore acts as a cushion to prevent large variations in systemic pressure.[35]

2. The stroke volume of the right heart is constant and is unaffected by intrathoracic pressure. All the above described changes are due to alterations of pulmonary vascular resistance which are caused by variations of intrathoracic pressure. Resistance is increased during inspiration, as a result of inflation of the lung, leading to decreased filling of the left ventricle.

This study does not attempt to decide which of these views is correct but strongly favors the first.

A. It is fortunate that the large respiratory variations in output of the right heart do not cause similar alterations in the output of left heart with consequent fluctuations of arterial pressure. Only in conditions severely limiting left heart output are these normal changes exaggerated to the point where the so-called "paradoxical pulse" becomes obvious. Their extent may afford a clinical index of certain functions of the pulmonary circulation and heart. Those individuals showing large variations in right heart output did not necessarily have large variations in the output of the left.

B. As has been suggested by Hamilton[12] part of the respiratory variation of blood pressure is due to direct transmission of changes of intrathoracic pressure through the large central blood vessels to the periphery. Consequently, intrathoracic pressure exerts a direct but small effect upon blood pressure. The primary cause of the respiratory variation of blood pressure, however, is probably cardiac in origin. If changes of blood pressure were due to intrathoracic pressure alone, one should obtain identical changes of systolic and diastolic pressures which closely followed the fluctuations of intrathoracic pressure. Diastolic changes were considerably smaller. The peaks of the changes of systolic pressure usually but not necessarily paralleled the position of the chest wall (if one can consider the pneumograph to follow intrathoracic pressure). In addition the variation of systolic pressure exceeded 5 mm. Hg, the normal respiratory change of intrathoracic pressure, in 10 patients of the series.

C. As deep inspiration is known to cause vasoconstriction[29, 30] it appeared conceivable that some neurogenic mechanism dependent upon respiration was affecting arteriolar size and, in turn, peripheral flow. It is not necessary, however, to postulate such a reflex. Application of the existing knowledge of the time of response of blood vessels to stimulation of an autonomic nerve[28] makes it unlikely that the variations of flow are neurogenic in origin. They are not abolished by the intravenous injection of tetraethylammonium chloride in doses sufficient to cause a pronounced fall of blood pressure in man,[31] but do disappear immediately on voluntary cessation of respiration. Thus it seems likely that the variations of flow are due to the changes of central blood pressure. The peripheral changes of flow in part cushion the changes of pressure.

Differences between Normotensive and Hypertensive Subjects

1. The finding that respiratory variations of the ballistocardiogram are on the average greater than normal in hypertensive subjects is similar to the experience of Brown and de Lalla,[32] and suggests that alterations in output of the right heart may be greater in hypertension. However, this disease can result in weakening of the left ventricle which is known to increase the respiratory variations of the ballistocardiogram.[23] *

2. The respiratory changes of left ventricular output were found to be smaller in the hypertensive group but this apparent difference is probably due to factors inherent in the calculations. A small error in the estimation of blood pressure at low levels gives greater increments of stroke volume by the pressure-pulse method than at hypertensive levels.[19]

3. Respiratory variations of blood pressure were on the average greater in the hypertensive group. This finding was to be expected because of the characteristics of the pressure volume curve of the aorta,[33] that is, a given increase

* Although no explanation is given for these findings,[23] the most plausible one is that the kinetic energy of the blood ejected by the left ventricle is reduced. Consequently the blood expelled by the right ventricle exerts a greater effect upon the size of the complexes. However in many instances these results may result, to a great extent, from the secondary effect of pooling of blood in the peripheral circulation and inadequate venous return to the heart.[24]

of volume causes a greater change of blood pressure at high than at low levels. As observed by others some of the changes of blood pressure were marked.[34]

4. The calculated changes of resistance indicated that the expiratory increase of peripheral blood flow cushioned the elevation of blood pressure in many normotensive individuals. In contrast, this occurred in only 3 of the hypertensive group (table 1). Apparently peripheral blood flow was not as readily increased. This finding is to be expected since peripheral resistance is elevated in hypertension. However, this interpretation is open to criticism.

Summary and Conclusions

1. During the inspiratory phase of quiet respiration in normotensive and hypertensive individuals (a) the size of ballistocardiographic complex grows larger, indicating an increase of right ventricular stroke index; (b) left ventricular stroke index, estimated by the pressure-pulse method, decreases; (c) blood pressure falls, systolic more than diastolic; (d) regional blood flow diminishes. The opposite changes occur during expiration.

2. The interrelationships of these changes are discussed.

3. It is suggested that the combined use of the ballistocardiographic and pressure-pulse methods provides a semiquantitative measure by which the respiratory variations of right and left ventricles may be separated.

4. The large respiratory variations in the output of the right heart are not correlated with those of the left. The discrepancy between the two may afford an index of clinical variations in the heart and pulmonary circulation.

5. Respiratory variations in regional blood flow are probably secondary to changes of arterial pressure, and are not under nervous control.

6. It is possible that the cushioning effect of the peripheral circulation is not normal in some cases of hypertension.

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CLINICAL PROGRESS

Editor: HERRMAN L. BLUMGART, M.D.

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Chronic Constrictive Pericarditis

By PAUL D. WHITE, M.D.

CHRONIC constrictive pericarditis, interestingly enough, was one of the very first pathologic conditions to be recognized. This is natural in view of the rather obvious gross lesion found at autopsy. Hence when the custom of postmortem examinations began to be established, pericarditis and its sequelae were quickly identified. Lower,[8] in 1669, described the clinical effect of interference of cardiac diastole by a constricting fibrous pericardium. Chevers,[4] however, in 1842, was the first to present clearly the clinical picture of chronic constrictive pericarditis. Wilks,[15] in 1870, further emphasized this syndrome. Curiously enough, however, it was Friedel Pick[10] whose name was attached many years later to the disease itself, which fact illustrates the neglect of the writings of our forebears.

An extraordinary delay supervened, following these early descriptions of the disease, before it was shown that the clinical diagnosis could be readily made and that surgical correction was feasible (White,[12] 1935). Although much is now known about chronic constrictive pericarditis and its treatment, new advances are likely to lead eventually to its reduction and to its earlier recognition and proper treatment.

INCIDENCE

Chronic constrictive pericarditis is still a rare disease but is being recognized more frequently. In a large hospital such as the Massachusetts General in Boston, several new cases are encountered each year. Doubtless with a reduction of tuberculosis the disease will become more and more rare.

From the Cardiac Department, Massachusetts General Hospital, Boston, Mass.

ETIOLOGY

For many years the cause of chronic constrictive pericarditis remained in doubt. Although it is still impossible in most cases to identify the etiology at operation or autopsy, it is quite certain in the opinion of many that the tubercle bacillus is the causative agent (Pickering,[11] Paul and co-workers[9]). Pickering has followed patients from the stage of acute tuberculosis of the pericardium to that of chronic constriction. Such an evolution, as a rule, takes many months or even a few years. The initial stage often is not observed. Observation of the initial stage will probably be possible more often in the future than in the past because of the institution of careful examination at the time of any acute illness in children and young adults. The active stage of tuberculous pericarditis may be readily overlooked. Malaise and slight fever may be the only symptoms, even in the presence of a large pericardial effusion which has developed so slowly that the body has accommodated itself. Children have actually been discovered at play with serious, acute, tuberculous involvement of the pericardium. This is quite different from the acute pericarditis of other cause, usually infectious, that is more likely to produce pain, rapid accumulation of fluid resulting in cardiac tamponade, and higher fever.

It is quite possible that other etiologic fac-

tors than the tubercle bacillus may infrequently result in chronic scarring of the pericardium with constriction. At one time pyogenic infections were blamed; they may continue to be factors in the future, especially with recovery from such serious illness made possible by antibiotic therapy. However, such etiologic factors exist almost certainly in but a small minority. The same is true of trauma which can produce hemopericardium; chronic constriction from such a cause is conceivable but must be very rare. Rheumatic fever, although frequently accompanied by pericarditis when there is pancarditis, does not result in chronic constrictive pericarditis. This can be stated quite definitely. Possibly there are rare exceptions but I myself have never encountered one. Rheumatic fever, to be sure, may leave pericardial adhesions, but these are not the massive constricting adhesions which we encounter after tuberculous infection. In only one case of some sixty with chronic constrictive pericarditis, have I noted a coincidental rheumatic valvular defect. In one other case there was a congenital septal defect. These coincidental lesions, however, may be expected in the population at large in occasional cases. The pericarditis associated with uremia and with myocardial infarction is not of the constricting type.

Pathologic Anatomy

Chronic constrictive pericarditis consists of fibrous thickening of visceral pericardium, of parietal pericardium, or of both surfaces, which are usually welded together by organization of the exudate which originally had been present in the sac itself. On occasion there may be slight, relatively unimportant, constriction by the fibrous parietal pericardium with very little involvement of the visceral pericardium; the reverse may also be true. In the average case, however, the pericardial sac is obliterated and both surfaces are involved about equally.

The fibrosed pericardium varies in thickness from 1 to 2 mm. up to 0.5 cm. or more. It also varies in distribution over the heart and great vessels, sometimes more in front over the right heart chambers and sometimes more in back over the left. As a rule, there is involvement around the entire heart and base of the great vessels, but some of the pericardium is frequently left rather thin and nonconstricting; there may be actual pericardial pockets free from involvement or containing residual fluid despite extensive fibrosis elsewhere. Although separate fibrous bands have been reported around the great veins or great arteries, these are much less common and important than the general involvement of the heart chambers themselves. There are, however, two areas of heart surface which may be importantly constricted. One is the right or left auriculoventricular groove, particularly the left, which produces a mechanical obstruction resembling mitral stenosis; the other is the interventricular groove, either along the course of the descending branch of the left coronary artery or in back adjoining the posterior coronary vessels. There may be actual interference with the coronary blood flow as a result of such contiguous pressure.

The laying down of calcium, sometimes in the form of granules like sand which may be loose in the pericardium, is a common complication of chronic constrictive pericarditis. Calcification is found in about one-third of the cases and at times results in the formation of massive plaques of calcium like a tortoise shell over large areas, filling the auriculoventricular grooves or even penetrating into the myocardium itself. It should be added, however, that in a few cases calcification of the pericardium without appreciable constriction may be found by x-ray study or at autopsy.

The myocardium itself may be relatively normal throughout the heart although there are two difficulties that should be noted. In the first place, subpericardial myocarditis with some chronic scarring is usually present to a varying degree. Secondly, there is an atonic state of the myocardium when it is encased rigidly in calcium which prevents its proper function. The muscle is there but it tends to be atrophic and at times is interspersed with scar tissue.

The size of the heart varies greatly. Classic chronic constrictive pericarditis has been said to be accompanied by a heart smaller than normal and atrophic. Although this is possible, it is more common to find some cardiac enlarge-

ment. To be sure, a slight increase of the heart shadow seen by x-ray can be explained by the thick pericardium, which may add 0.5 cm. to each border of the heart shadow, but various strains on the heart and perhaps the diastolic fixation of some of the heart by the scarred pericardium explain the enlargement that is frequently found. Such enlargement is not great, as a rule, and the heart may be only slightly above normal in volume or weight. There are a few instances where the right ventricle is much larger than usual as a result of constriction of the left heart chambers, causing a disease picture much like that in mitral stenosis. The auricles may also be more capacious than normal, whether they are involved in the constricting process or not. The valves are usually normal, although there may be insufficiency resulting from dilatation of the ventricular cavities.

Chronic constrictive pericarditis is occasionally accompanied by chronic constricting pleuritis[3] and even chronic fibrous peritonitis. Such concomitant lesions indicate the primary occurrence of polyserositis, also doubtless tuberculous in origin. The thickened peritoneum over the liver is due not to the engorgement of the liver itself in so-called Pick's disease but rather to the occurrence of acute peritonitis at the time of the acute pericarditis followed by residual fibrosis.

Pathologic Physiology

Little need be said about the pathologic physiology of chronic constrictive pericarditis. It was quite simply explained centuries ago by Lower and again over a hundred years ago by Chevers. The difficulty consists mainly in the inability of the heart to assume its proper size in diastole and to contract properly in systole, that is, there is a mechanical interference with the normal systole and diastole, especially the latter. Thus, the blood cannot enter the heart properly and is backed up in the great veins and liver and sometimes in the pulmonary blood vessels. There is also an insufficient output of blood, causing a certain amount of forward failure for which the muscle is not primarily responsible.

When the left heart chambers are preponderantly involved there is, as in mitral stenosis, an increase in pulmonary blood pressure which should be measured in every case by cardiac catheterization. The determination of the pulmonary blood pressure is important because it aids in the decision on surgical technic. If the pulmonary blood pressure is increased in chronic constrictive pericarditis, the surgeon should release the left heart chambers first; in such cases the surgical approach must be so arranged as to reach the back of the heart primarily.

If the right heart chambers are preponderantly constricted, there is naturally engorgement of the neck veins and liver, with relatively little pulsation evident. On the other hand, when the right heart fails because of constriction of the left heart chambers, then there tends to be a vigorous systolic jugular pulse and some pulsation of the liver, as in any case of total heart failure, except that in cases of chronic constrictive pericarditis the deep systolic pulsation becomes chronic and may continue for years, simulating the effect of tricuspid valve disease.

With diminution in the output of the heart, which is not uncommon, the blood pressure, especially the pulse pressure, tends to be low. It is not unusual to find the systemic blood pressure to be 100 mm. Hg systolic and 80 diastolic.

Both the irritation of the heart by the actual process involving the myocardium and the effect of constriction of the left heart chambers on the right ventricle and right auricle result not infrequently in auricular arrhythmias. Auricular fibrillation and less commonly auricular flutter occur as complications in chronic constrictive pericarditis. About a third of our cases have shown such arrhythmias, which add an increased burden to the heart; in such patients there must be control of the heart rate by digitalization.

Symptoms

The symptomatology of chronic constrictive pericarditis can be prophesied and simply explained when one understands the pathologic anatomy and physiology of this disease. It is, of course, of much interest to recognize the

initial acute pericarditis which is usually attended by malaise, some febrile reaction, and not infrequently some evidence of cardiac tamponade from a pericardial effusion.

The acute tuberculous pericarditis may be primal per se or as a result of the complication of miliary tuberculosis. On the other hand, it may pass insidiously from the acute to the subacute and finally to the chronic stage. A year or two or three may elapse between the occurrence of the acute pericarditis and the beginning of evidence of chronic constriction. Sometimes the disease is discovered accidentally during routine examination for insurance or for military service, particularly when x-rays reveal calcification of the pericardium or when the astute observer notices a little increase in jugular pulse or enlargement of the liver or looks for the cause of an unexplained arrhythmia.

Actually there are very few symptoms of chronic constrictive pericarditis. The signs are more important. Dyspnea can occur if the left heart chambers are preponderantly affected, as in mitral stenosis, with engorgement of the lung vessels and decrease in vital capacity, but more commonly the liver enlarges and the abdomen increases in size causing discomfort to the individual affected. There may even be a little ascites before much attention is paid by the patient to his disease. Less commonly there is unexplained swelling of both legs early in the clinical course. The liver enlargement and ascites are more prominent than is edema of the legs. Fever occurs only if there is acute or subacute infection or recurrence thereof. Pain, as a rule, is absent and palpitation is not noted except in a few instances of tachycardia secondary to auricular fibrillation or flutter.

Signs

The signs of chronic constrictive pericarditis allow the diagnosis to be made readily in most instances. When, in the absence of clearcut etiology of the ordinary causes of heart disease such as congenital defects, rheumatism, hypertension, and coronary atherosclerosis, with little enlargement of the heart and usually normal rhythm, the neck veins are found to be full and the liver enlarged, one should think at once of the possibility of chronic constrictive pericarditis. The presence of ascites makes this even more likely. Heart murmurs are not the rule. On occasion there may be a systolic murmur at the apex associated with some mitral regurgitation or at the lower end of the sternum associated with tricuspid regurgitation, but important murmurs are invariably lacking. The pulmonary second sound may be increased if there is pulmonary hypertension. This is, however, found in the minority of the cases. In patients with dilated right ventricle a third sound may be heard along the left border of the sternum indicative of right ventricular enlargement. The lungs are generally clear, although in advanced cases there may be right hydrothorax, or pleural adhesions secondary to chronic concomitant tuberculous pleuritis. A complication that may be serious is that of engorgement and varicosities of the leg veins with possible thromboses. If arrhythmia is present, there may be a rapid regular or rapid irregular pulse rate and the blood pressure tends, as already stated, to be low with a small pulse pressure. The venous pressure, on the other hand, is very much elevated, frequently exceeding 200 mm. of water and on occasion even exceeding 300 mm. One other important sign in advanced cases is that of the paradoxical pulse, the blood pressure decreasing even to the point of disappearance during inspiration in some of the more advanced cases.

X-ray Examination

Usually the heart shadow on the x-ray film or seen with a fluoroscope is abnormal but there are a few instances in which little or nothing wrong can be found in the constricted heart. Cardiac pulsation is decreased as a rule, sometimes over one part of the heart shadow more than another. The heart varies in size and position. There may or may not be calcification. In about a third of the cases, bands of calcium can be seen, better in the oblique than in the anteroposterior view. The sheets of calcium are better seen end on, of course, than when viewed at right angles to the surface. Small areas of calcification may be undiscoverable by x-ray examination.

Electrocardiography

The electrocardiogram is usually very revealing; it shows a fairly distinct pattern of pericardial nature with lowering of voltage in most limb and precordial leads, and abnormality of the T waves without much change in the QRS complexes except for decreased voltage. The T waves tend to be flat or slightly inverted in all limb and precordial leads. The electrocardiographic pattern in chronic constrictive pericarditis is generally easily distinguishable from that produced by coronary heart disease. Arrhythmias are, of course, well shown.

One of the interesting evolutions of the electrocardiogram in cases that are observed for a long time is the development of evidence of right ventricular preponderance, sometimes accompanied by the onset of auricular fibrillation or flutter, when the constriction of the left heart chambers produces steadily increasing enlargement of the right ventricle. This is a telltale clue.

Cardiac Catheterization

An important new technic which I would now consider essential to the study of any case of chronic constrictive pericarditis is determination of the pulmonary blood pressure by cardiac catheterization. Normally the systolic pressure in the right ventricle and pulmonary artery does not exceed 25 mm. Hg. If there is preponderant constriction of the left heart chambers, the pulmonary blood pressure may be twice or thrice the normal. As an aid to determining which part of the heart is most involved and, from this, the surgical approach, knowledge of the pulmonary blood pressure is of great help.

Course and Prognosis

Chronic constrictive pericarditis varies in its course from that of a fulminating disease, resulting in hopeless invalidism and death within a relatively few months or a year or two, to a chronic condition that causes relatively little disability and does not shorten life. In the average case the disease continues for ten to twenty years, unless some serious complication occurs to shorten life or unless, more optimistically, a cure is effected by surgical intervention. Before surgical therapy was introduced, I remember having followed several individuals for a decade or more who needed abdominal paracentesis perhaps once a month. Successful surgical treatment can apparently restore normal health and full length of life. The first case successfully treated by surgery in the United States, reported by Dr. Churchill and me[14] over twenty years ago, has continued in excellent health so far as the circulatory apparatus is concerned. She is now 40 years old, a well and active woman who has raised a family.

One other patient may be cited to illustrate the occasional unimportance of the condition. A doctor practicing in Nova Scotia came to see Dr. Churchill and me in 1930; he showed evidence of chronic constrictive pericarditis of slight to moderate degree. He was then 57 years old. He gave a history of acute pericarditis of unknown nature while he was at Johns Hopkins Medical School in Baltimore in 1894. He began medical practice in Nova Scotia but after a few years, noticing some enlargement of the liver, he came to the Massachusetts General Hospital for study and there was diagnosed as having liver disease, probably cirrhosis, of unknown origin. When we examined him in 1930 we found him in fairly good health and, because of his age and relative well being, advised against surgical intervention. He continued to practice until 1939 and died in 1948 at the age of 76.

Treatment

Until about 20 years ago the treatment of chronic constrictive pericarditis was very discouraging. It consisted in efforts to keep the congestion under control. This congestion was often represented by general anasarca with preponderant liver enlargement and ascites. Not infrequently it was necessary to perform regular abdominal paracentesis. Although Finsen[7] had shown that restriction of salt and fluid was effective in controlling the ascites, it was not customary years ago to advise a low sodium intake. Digitalis was known to be ineffective. Some diuretics were employed.

Since 20 years ago, both medical and

surgical treatments have improved greatly. Some individuals who are too old or too seriously involved to permit surgery are benefited by medical measures; any victim of the disease with tachycardia due to auricular flutter or to auricular fibrillation is better with a control of the heart rate by digitalis, whether or not surgical therapy is also employed. Since the advent of mercurial diuretics and strict low sodium diets, some patients can be kept reasonably comfortable without surgery, but the majority of patients are still in need of and are benefited by pericardial resection. A few mild cases, such as the Nova Scotian physician already referred to, can get along without surgery and with moderate medical measures.

The surgical treatment of chronic constrictive pericarditis was first recommended by Delorme in 1898,[5] but the operation was not performed until some years later. A few cases were operated upon in Germany in the early part of the century, but only in the last twenty years has surgery become the routine method of choice. Pericardial resection, which is very different from Brauer's[2] operation of freeing the heart from the thoracic cage, is a delicate, time-consuming procedure, somewhat hazardous, but under modern conditions of expert anesthesia and thoracic surgery no longer the dreaded ordeal that it was many years ago.

When surgery was first utilized for chronic constrictive pericarditis, it was the custom to approach the heart anteriorly and to free the right heart chambers. Even at that time, however, it was realized that if the whole heart were affected it would be wise to decorticate the left heart chambers first. Surprisingly, the majority of patients who were operated upon during the first few years of pericardial surgery were successfully treated through the anterior approach. As time went on, however, it became evident that occasional failures were due to the inadequate freeing of the heart over the anterior chambers only.[13] Hence of late years decortication of both ventricles has been found advisable, either by a lateral approach or best by splitting the sternum and opening the thorax wide. Most observers now agree that it is wisest to free the left heart chambers first even if a second operation is necessary to release the anterior heart chambers. Cardiac catheterization with a determination of the pulmonary blood pressure is very helpful in indicating at once whether it is necessary to decorticate posteriorly first. With an elevated pulmonary blood pressure, the first attack should be on the left heart chambers.

Details of the pericardial resection can be found in the writings of Beck, Churchill, Sweet, and others.

Complications during or after operation can be disturbing. On several occasions the heart wall has actually been punctured, with resultant vigorous bleeding. However, rents in the auricle or ventricle can be and have been repaired, with survival and much improved health postoperatively. Rarely, especially if there is subacute activity of the process, there may be a draining fistula which tends to close with time. In a few instances there have been venous or intracardiac vascular thromboses with resultant pulmonary or peripheral embolism. There has been persistence of congestion in some cases as a result of either inadequate freeing of the heart or failure of the right ventricle after it has been freed or disturbing arrhythmia.

Undoubtedly, with still further improvement in preoperative preparation and surgical technics, there will be a still greater percentage of clinical cure, complete or partial. In a series of cases of chronic constrictive pericarditis seen at the Massachusetts General Hospital, a recent report[9] has given the following figures: In the period 1914 through May 1947, 53 patients with constrictive pericarditis had been seen. Surgical exploration with pericardiolysis and partial pericardiectomy was undertaken on 42 of these patients. The results in 25 (60.9 per cent) have been excellent, good, or satisfactory. Six patients died as a result of the operative procedure itself, 5 died from complicating disease, and 4 died from the effects of their underlying disease. The cause of death of one patient is not known. Seven patients were too ill for surgery and died while receiving medical treatment. One patient died before the operative series began, 2 patients had such minimal symptoms that operation was felt to be unnecessary, and one patient has not been followed.

Differential Diagnosis

There are three conditions with which chronic constrictive pericarditis has been readily confused, although careful study should reduce very much such confusion in the future. These three conditions include: (1) cirrhosis of the liver in which, although there may be ascites, the venous pressure is normal and the neck veins are not engorged; (2) heart failure in which there is, as a rule, obvious disease of the heart itself by rheumatic involvement, hypertension, or coronary atherosclerosis; (3) myocarditis with failure of unknown cause in which there is, as a rule, much more cardiac enlargement, no evidence of pericarditis per se, and a different electrocardiographic pattern.

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ABSTRACTS

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BACTERIAL ENDOCARDITIS

Curtin, M.: Chloramphenicol in Subacute Bacterial Endocarditis. Lancet **2:** 804 (Dec.), 1950.

The author describes a case of subacute bacterial endocarditis occurring in a rheumatic heart of a 25 year old pregnant female and caused by *Streptococcus viridans*. Early treatment with penicillin for over two months appeared effective, but eight days after therapy had ended there was definite relapse. Because of Chloramphenicol sensitivity of the cultured *Str. viridans* she was then given Chloramphenicol 0.5 Gm. every four hours for 22 days. The rapid disappearance of the offending organisms from the bloodstream during treatment and the corresponding rapid improvement in the sedimentation rate suggest that this patient was "cured" by the Chloramphenicol. Follow-up studies after six months revealed no recurrence of disease.

BERNSTEIN

Spies, H. W., Dowling, H. F., and Lepper, M. H., Wolfe, C. K., and Caldwell, Jr., E. R.: Aureomycin in the Treatment of Bacterial Endocarditis. Arch. Int. Med. **87:** 66 (Jan.), 1951.

The authors treated nine patients with endocarditis caused by alpha and beta streptococci, pneumococci and staphylococci with aureomycin. Two patients recovered with aureomycin therapy; one recovered after receiving combined aureomycin and penicillin therapy, and one failed to show improvement with aureomycin therapy but recovered when he received penicillin. Of the 5 patients who died, one had extensive miliary tuberculosis and the others had either ruptured valve cusps or congestive heart failure which accounted, at least in part, for the fatal outcome.

In vitro studies of the synergistic action of aureomycin and penicillin were utilized as a guide to the treatment of one patient.

It is concluded that aureomycin is a valuable agent in the treatment of endocarditis, either alone or in combination with penicillin.

BERNSTEIN

Hoffman, M. S., Wellman, W. E., and Sayre, G. P.: Escherichia Coli Endocarditis: Report of Case. Proc. Staff Meet. Mayo Clin. **68:** 1 (Jan.), 1951.

The authors report a fatal case of *Escherichia coli* endocarditis occurring in a 69 year old female and diagnosed about three months postcholecystectomy. The blood stream of this patient was repeatedly sterilized by Terramycin. However, subsequent consistent reappearance of the organisms in the blood was evidence that persistent localized infection was present somewhere in the body with easy access to the blood. Necropsy revealed that the major site of such infection was the mitral valve. Had the organisms been confined to the blood stream and had they not invaded the endocardium, this patient would probably have recovered.

As opposed to the usual types of endocarditis, *Escherichia coli* invasion of the endocardium may occur in the absence of previous cardiac damage. The mortality rate in reported cases of *Escherichia coli* endocarditis is 100 per cent, even with the advent of newer antibiotics.

SIMON

BLOOD COAGULATION

Von Hueber, E. F.: The Treatment of Coronary Thrombosis and Fresh Myocardial Infarction with a New Anticoagulant Tromexan. Cardiologia **17:** 223 (Fasc. 3/4), 1950.

The author presents 21 selected cases of acute infarction and 9 cases of coronary failure with impending infarction which were successfully treated with Tromexan, a derivative of dicumarol. In the first group no thromboembolic complications were found and all patients survived. In the second group, a case of fatal myocardial infarction developed nine weeks later, and in another patient death occurred through infarction when Tromexan treatment was omitted after coronary failure had subsided. The author believes that this new drug acts more quickly and has less cumulative action than dicumarol. No side effects were noted.

WAIFE

Cosgriff, S. W., Diefenbach, A. F., and Vogt, W. Jr.: Hypercoagulability of the Blood Associated with ACTH and Cortisone Therapy. Am. J. Med. **9:** 752 (Dec.), 1950.

Eleven thromboembolic complications in 175 patients treated with ACTH or cortisone prompted the writers to study the effect of these two drugs on the blood coagulation mechanism of humans. Changes in the venous clotting time and in the heparin-retarded venous clotting time indicated that these drugs frequently produced hypercoagulability of blood. No significant changes were noted in the prothrombin time, the fibrinogen B content, or protamine titration. Prophylactic anticoagulant therapy may be advisable in some patients receiving ACTH or cortisone.

HARRIS

CONGENITAL ANOMALIES

Morse, M., Cassels, P. E., and Holder, M.: The Position of the Oxygen Dissociation Curve of the Blood in Cyanotic Congenital Heart Disease. J. Clin. Investigation **29:** 1098 (Aug.), 1950.

The authors performed studies on oxygen dissociation in 29 patients with cyanotic congenital heart disease and compared their findings with 43 normal individuals. Using the in vitro tonometer method it was found that the oxygen dissociation curve tends to be displaced to the right compared with normals. Such a displacement appears to be a compensatory mechanism to reduce tissue hypoxia. By promoting the dissociation of oxyhemoglobin, the mean capillary oxygen pressure for a given degree of arterial and venous unsaturation is increased, and diffusion of oxygen through the capillaries is facilitated. While the increase in oxygen tension for a given percentage saturation is comparatively small, it is of the same order of magnitude as the displacement measured in blood of the residents of high altitudes. The displacement is greater in cyanotic individuals with pulmonary stenosis than in those without the stenosis and the displacement decreases after surgical anastomosis between the pulmonary artery and aorta.

WAIFE

Robinson, Jr., E. B.: Anesthesiology in Congenital Heart Disease. J.M.A. Alabama **20:** 85 (Sept.), 1950.

The author states that a patient with tetralogy of Fallot is a poor surgical risk. The extreme hypoxia of children with tetralogy of Fallot, even at rest, makes them difficult anesthetic problems preoperatively. Preoperative morphine, even in large doses, is used for its sedative effect in order that these patients can utilize oxygen more efficiently. Large doses of atropine are used with the morphine to suppress secretions and, most important, to depress the parasympathetic nervous system in order to obviate or at least to minimize any untoward reflexes during the surgery.

It is desirable to use the anesthetic agent that permits a rapid and smooth induction with high oxygen tension, one which will permit close control of the depth of anesthesia. These patients should have an adequate airway so that the lung may be collapsed or expanded instantly. The method should be one that has no excess carbon dioxide, one that will permit a rapid return to consciousness and most of all will cause as little further disturbance of the physiology as possible. The author uses an induction with cyclopropane; once the anesthesia is established, an endotracheal tube is placed in the trachea. The endotracheal tube is directly connected to a to-and-fro soda lime absorber in order to remove the carbon dioxide from the atmosphere. Ether is gradually added, so that very shortly the patient receives only ether and oxygen. Ether will better obtund the undesirable reflexes than will cyclopropane. Undesirable reflexes are more apt to occur during the progress of surgery, especially when the great vessels are handled and when the surgeon is close to the hilum of the lung. Once anesthesia is established, very little ether is needed for maintenance and the patients would react shortly after the operation is completed. An ice bag should be placed in the soda lime absorber to diminish the amount of heat generated, because these children tolerate increased temperatures very poorly.

An infusion of saline is started preoperatively and this is replaced by blood plasma when actual surgery starts. Blood plasma is used to replace the volume lost during surgery. The blood plasma suffices since most such patients have polycythemia.

MINTZ

Gasul, B. M., Fell, E. H., Maurelis, W., and Casas, A.: Diagnosis of Tricuspid Atresia or Stenosis in Infants. Pediatrics **6:** 862 (Dec.), 1950.

The authors divide tricuspid atresia or stenosis into two large groups. The patients in Type I, in addition to the atresia or stenosis, have either a patent foramen ovale or an interauricular septal defect, hypoplasia or absence of the right ventricle, and hypoplasia or atresia of the pulmonary artery. A patent ductus arteriosus or an interventricular

septal defect may or may not be present. These patients are considered amenable to surgery, whereas the patients in Type II are not. In addition to the atresia or hypoplasia of the tricuspid valve, Type II patients have an interauricular communication, hypoplasia of the right ventricle and complete transposition of the great vessels. They may also have a patent ductus arteriosus, or interventricular septal defect, or both. The pulmonary artery is usually larger than the aorta because the pulmonary artery originates from the large left ventricle and the aorta from the hypoplastic right ventricle. Hemodynamically, in Type I, there is only a small amount of blood entering the pulmonary artery, whereas in Type II, the blood reaching the aorta is poorly oxygenated.

In Type I cyanosis appears early in life, and later becomes intense. The heart is not much enlarged on percussion. There is a concavity in the region of the pulmonary conus and the vascular pulmonary markings are diminished. The angiocardiogram shows the dye entering the left auricle directly from the right auricle and the right ventricle cannot be seen on the first film.

In Type II, the cyanosis is less marked. The heart is considerably enlarged, being primarily left ventricular. There is also a concavity at the pulmonary conus, but the pulmonary markings are exaggerated and on fluoroscopic examination, pulmonary vascular pulsations can be seen. The angiocardiogram is similar to that of Type I except the pulmonary artery and aorta are transposed. Both types show a left axis deviation on the electrocardiogram.

The authors stress the importance of making an early diagnosis of tricuspid atresia in differentiating the two types of this malformation.

MARGOLIES

Sellors, T. H., and Belcher, J. R.: Surgical Relief of Congenital Cyanotic Heart Disease, Late Results in 72 Cases. Lancet **2**: 887 (Dec.), 1950.

A series of 93 patients have been operated on for congenital cyanotic heart disease. There were nine deaths consequent upon the operation, but the mortality was proportionately higher in the early cases than in the more recent ones. The majority of cases were examples of Fallot's tetralogy.

The technic adopted in most cases was the performance of a left end-to-side Blalock type of anastomosis between the pulmonary and subclavian arteries using a posterolateral approach. The pericardium was routinely opened and the heart and site of the stenosis examined. The end results as judged through periods ranging from six months to two and a half years were gratifying. One patient died suddenly a year after operation, and seven were regarded as not improved, but very marked benefit was obtained by 42 patients who were previously severely disabled, and a further 22 gained considerable benefit in exercise tolerance and general health.

BERNSTEIN

Jordan, R. A., Dry, T. J., and Edwards, J. E.: Anomalous Origin of the Right Coronary Artery from the Pulmonary Trunk. Proc. Staff Meet., Mayo Clin. **25**: 673 (Dec.), 1950.

A case in which anomalous origin of the right coronary artery from the pulmonary trunk occurred in a 74 year old man is reported. Two other similar reported cases are reviewed. No disability seems to be caused by the anomaly. It is suggested that in the presence of this malformation the left coronary artery acts as though a single coronary artery were present, while the right one acts as a vein, carrying blood centrally to the pulmonary trunk.

In contrast to anomalous origin of the right coronary artery, anomalous origin of the left coronary artery from the pulmonary trunk is more common, and frequently is associated with significant myocardial ischemia. In 27 such cases reviewed, 20 patients died at the age of 13 months or younger.

A well-defined clinical syndrome associated with pulmonary origin of the left coronary artery is described in which the infant generally appears to be normal at birth and for some time therafter. This is followed by attacks, often at feeding time, characterized by acute discomfort, short respiratory excursions and grunts. These are followed in turn by sweating and apparent shock. It is felt that the attacks are evidence of angina pectoris. The roentgenogram shows evidence of cardiac enlargement and the electrocardiogram may reveal evidence suggestive of myocardial hypoxia.

SIMON

Segers, M., and Brombart, M.: Double Aortic Arch. Acta Cardiol. **5**: 623, 1950.

The authors present roentgenologic data proving the presence of a double aortic arch in a 58 year old woman without clinical symptoms typical for this anomaly. A chest film in the posteroanterior view showed a circular shadow at the level of the aortic knob which could have been mistaken for a mediastinal tumor. Studies in the oblique views revealed encroachment upon the barium-filled esophagus anteriorly as well as posteriorly at the usual level of the aortic arch. An additional anomalous right sided aortic impression of the barium shadow was seen above the diaphragm indicating right sided position of the lower part of the descending thoracic aorta.

PICK

CONGESTIVE HEART FAILURE

Iseri, L. T., Boyle, A. J., and Myers, G. B.: Water and Electrolyte Balance during Recovery from Severe Congestive Failure on a 50 Milligram Sodium Diet. Am. Heart J. **40**: 706 (Nov.), 1950.

The purpose of this study was to determine the clinical efficacy of a 50 mg. sodium diet in severe cardiac failure, and to investigate balances of water, sodium, potassium, chloride, and nitrogen during recovery. The diet consisted of 2000 ml. of Lanolac formula, 500 ml. of orange juice, 30 Gm. of sugar and crystalline vitamins. Seven of 9 patients with congestive heart failure given the diet tolerated it for the study, ranging from 8 to 16 days. The major lesion was rheumatic mitral stenosis in 4 patients, and hypertensive and/or arteriosclerotic heart disease in 3. Prior to the institution of this special diet, congestive failure had proved refractory to standard regimen consisting of bedrest, low sodium diet, digitalis and mercurial therapy.

The extracellular volume decreased more in the 4 patients with marked peripheral edema than in the 3 with no clinically detectable edema, that is, 8.28 liters and 1.44 liter respectively. The elimination of water and chloride was in accordance with the plasma chloride concentration. In 2 patients with initially normal plasma levels, chloride and water were lost from the extracellular space in isotonic proportions, whereas less chloride was lost in the 5 patients with initial hypochloremia. Plasma sodium concentrations were initially elevated in 4 patients and normal in 3, and maintained a plateau during recovery from congestive failure, indicating parallelism in losses of extracellular sodium and water, even in the presence of hypernatremia. In 6 patients there was a positive nitrogen balance. During recovery from congestive failure the intracellular compartment lost water (average 1325 ml.), but gained potassium and sodium (average 234 mEq.). The cellular uptake of nitrogen and potassium and loss of water during recovery from congestive failure were similar in direction to the changes that would have been expected with a return to normal function from adrenal cortical hyperactivity as a result of the stress reaction.

The findings in this study are in accord with the hypothesis that the development of congestive heart failure is accompanied by an alteration of cellular metabolism, manifested by liberation of ionized base from osmotically inactive constituents of the protoplasm, followed by shifts of potassium and sodium out of the cells and water in the opposite direction to maintain osmotic equilibrium with the extracellular compartment. Recovery from congestive failure is accompanied by cellular release of water and uptake of potassium and sodium, with coincident osmotic inactivation of cell base.

HELLERSTEIN

CORONARY ARTERY DISEASE, MYOCARDIAL INFARCTION

Weinberg, S. L., Reynolds, R. W., Rosenman, R. H., and Katz, L. N.: Electrocardiographic Changes Associated with Patchy Myocardial Fibrosis in the Absence of Confluent Myocardial Infarction. Am. Heart J. **40:** 745 (Nov.), 1950.

The authors studied the electrocardiograms of 95 patients whose hearts at autopsy showed moderate to marked, disseminated, patchy myocardial fibrosis without confluent myocardial infarction. The electrocardiograms consisted of the standard limb leads and three precordial leads. In 67 patients the myocardial fibrosis was of the degree which might be expected from the amount of coronary sclerosis and stenosis found. In 28 patients the degree of fibrosis was greater than the coronary disease might warrant. In 15 of the latter, there was considerable left ventricular hypertrophy which might account for the excessive fibrosis. Only one normal electrocardiogram was noted in this series. In general the more marked electrocardiographic changes were observed in the cases with marked myocardial fibrosis. In only 3 patients did the patterns simulate myocardial infarction. Since most of the electrocardiographic changes are not specifically diagnostic of chronic coronary insufficiency, it would not seem appropriate to make such an interpretation merely from the electrocardiogram, unless evidence of previous confluent infarction would be observed. Nevertheless, in older persons, these electrocardiographic changes are usually caused by the patchy myocardial fibrosis consequent to chronic coronary insufficiency.

HELLERSTEIN

Tatiboute, L., and Mathivat, A.: Myocardial Infarction and Disturbances of Rhythm. Arch. d. mal. du coeur **43:** 981 (Nov.), 1950.

Disturbances of the cardiac rhythm are infrequent in the course of myocardial infarction and were found by the author in 8 per cent of his observations, prevalently in males over 50 years. The actual incidence of arrhythmias is probably higher, since they may be transient and escape clinical and electrocardiographic recognition. Arrhythmias observed most frequently were auricular fibrillation, premature beats and ventricular tachycardia. Out of 37 cases, 30 showed involvement of the intraventricular septum by the infarct.

Digitalis therapy instituted in 10 instances led to marked improvement without any complication. Ephedrine gave variable results in cases with Stokes-Adams syndrome as a result of conduction disturbance. Quinidine failed in 4 out of 6 cases of ventricular tachycardia to prevent a fatal outcome.

PICK

Tedeschi, C. G., Stevenson, T. D., Jr., and Levenson, H. M.: Abscess Formation in Myocardial Infarction. New England J. Med. **243:** 1024 (Dec.), 1950.

Two cases exhibiting an extremely rare complication of myocardial infarction are presented. In both, abscess formation and pathogenic organisms (a coagulase-positive hemolytic *Staphylococcus aureus*) were found at postmortem examination at

the site of a recent myocardial infarct. In both cases, similar organisms were isolated from areas of concomitant bronchopneumonia. The authors suggest that the septic foci in the myocardium resulted from the invasion of a primarily bland infarct by circulating microorganisms.

SAGALL

Lodge-Patch J.: The Ageing of Cardiac Infarcts and Its Influence on Cardiac Rupture. Brit. Heart J. **13**: 37, 1951.

The author reports the sequence of histologic changes in infarcts of the myocardium and estimates the period at which hemopericardium is likely to occur based upon a study of eighteen unruptured infarcts with a clear history of the onset of infarction and of ten infarcts complicated by hemopericardium. Grossly, the infarct is pale and edematous in 15 hours, in 36 hours a hemorrhagic border appears, in one week the center is rubbery and the infarct is slightly shrunken. Thinning of the myocardium occurs in three weeks.

Microscopically, nuclear degeneration appears in five hours and neutrophilic infiltration in six hours. These increase until in 48 hours they are abundant at the periphery of the infarct. They may be seen up to five days. Necrosis of leukocytes appears in two days and their basophilic degenerated products are seen separating the muscle fasciculi. Myocardial cytoplasmic hyalinization with eosinophilic changes is seen in four to six days. Mononuclear cells that appear on the fourth day reach their maximum in six weeks. Phagocytized pigment is seen within these cells on the ninth day. Lymphocytes with plasma cells also appear on the fourth day and reach their maximum in three weeks. Eosinophils appear on the seventh day and are also abundant in the third week. Fibroblasts and newly formed capillaries may appear on the fourth day and are abundant from the third to the sixth week.

Rupture of the infarct was estimated to occur from the first to the fourteenth day.

The author concludes that the age of an infarct can be judged from its histologic appearance within a range of 24 hours during the first week and of wider range at later stages.

SOLOFF

Muller, O., Humerfelt, S., Rasmussen, H., and Storstein, O.: Perforation of the Ventricular Septum following Myocardial Infarction. Acta Cardiologia **5**: 633, 1950.

A 58 year old man developed 10 days after onset of symptoms of myocardial infarction a loud systolic murmur at the left side of the lower sternum. Five months later, the electrocardiogram showed right bundle branch block with inversion of the T wave in II and III, and a marked enlargement of the cardiac silhouette. The presence of an interventricular septal defect was proven by cardiac catheterization, which revealed equal systolic pressures in right and left ventricle and an increase of the oxygen saturation of more than 3 per cent between right auricle and ventricle, due to a calculated left to right shunt of 5.2 liter per minute.

The patient died 15 months later in congestive heart failure. At autopsy the right coronary artery was obliterated by atheromatous plaques and old scars were found in the posterior wall and in the upper and posterior portion of the interventricular septum. In the latter scarred area, nine perforations could be demonstrated, 2 to 5 mm. in size.

PICK

ELECTROCARDIOGRAPHY

Meyer, P., and Schmidt, Cl.: The Significance of Unipolar Dorsal Leads (with Special Reference to Leads V8L) in the Diagnosis of Posterior Infarction. Arch d. mal. du coeur **43**: 903 (Oct.), 1950.

The authors present studies on the direction of the spatial vector of the T wave in normals and in patients with posterior wall infarction, determined with the help of "unipolar" leads taken from the right and left side of the back at three different levels. The T vector in normals has a left to right, downward and forward direction; in the presence of posterior wall infarct it points upward, forward and from right to left. A lead from the left side of the back (V_{8L}) is, therefore, in the latter condition, located in the negative field of this vector. In 20 cases of typical recent posterior wall infarction, lead V_{8L} showed a significant inversion of the T wave, which was also present in this lead in 5 cases of remote posterior wall infarction with uncharacteristic limb leads. In contrast to it, T was found consistently upright in V_{8L} in normals and in cases who had inverted T waves in lead III, but showed no clinical evidence of coronary disease.

PICK

Sandberg, A. A., Wener, J., and Scherlis, L.: Left Ventricular Cavity Potentials in Induced Left Bundle Branch Block Studied with Esophageal Leads. Am. Heart J. **40**: 531 (Oct.), 1950.

The authors studied the changes in the QRS complexes of precordial and esophageal leads reflecting left ventricular cavity potentials during periods of transition into and out of left bundle branch block. The studies were conducted on a 43 year old woman who developed constrictive substernal chest pain and palpitation, usually occurring after effort and relieved by nitroglycerin. Left bundle branch block consistently developed after a double two step exercise test, or the inhalation of amyl nitrite. This was associated with an increase of the heart rate to a critical level (R-R interval from 0.50 to 0.57 second). Inhalation of 10 per cent oxygen and 90 per cent nitrogen produced significant RS-T segment displacement, but no change in

heart rate or conduction. The period of transition from normal conduction to left bundle branch block was characterized by the appearance of RS instead of QS complexes in esophageal leads reflecting left ventricular cavity potentials. On four occasions there was a gradual transition from the QS pattern to the RS pattern. The occurrence of such transition patterns was similar to that produced by Sodi-Pallares and co-workers in animals. These transitional patterns offer proof for the occurrence of partial bundle branch block comparable to partial atrioventricular block with progressively increased P-R interval. The transient character of the left bundle branch block in the present study (20 to 46 seconds) demonstrates that defective conduction in the bundle branches may be due to physiologic and functional alteration in the conducting system rather than to a specific anatomic lesion.

HELLERSTEIN

Mechelke, K., and Meitner, H. J.: The Electrocardiographic Pattern of Vagal Regulations Under Pharmacologic and Physiologic Stress. Arch. f. Kreislaufforsch. **16:** 161 (Oct.), 1950.

Intravenous injection of a sympathomimetic drug produces in man a biphasic reaction. The immediate "sympathetic" effect consists in increase of the venous pressure and acceleration of heart rate and respiration and is mediated by the Bainbridge reflex. This is followed by a phase of vagal counter-regulation with bradycardia and increase of blood pressure amplitude.

The authors studied the extent of this double reaction in the electrocardiograms of 3 vagotonic and of 4 sympathotonic normal persons, using for sympathic stimulation adrenaline, sympathol, ephedrine or veritol. The degree of the vagal phase was compared with the effect of "physiologic" vagal stimulation (ocular pressure and a modified and standardized Valsalva test). The counter-regulatory vagal phase of sympathetic stimulation as well as the response to physiologic vagal stimulation was found to be marked in persons with signs of increased sympathetic tone, producing considerable bradycardia and nodal escape. Vagotonic persons showed a similar marked response to ocular pressure and Valsalva test, but failed to show a significant vagal phase following sympathetic stimulation. The occurrence of the latter phenomenon seems, therefore, to depend on the vegetative structure of the examined individual.

PICK

Papanicolis, I., and Vlachoyannis, S.: Considerations on the Deviation of the Ventricular Gradient (G) in Myocardial Infarction. Arch. d. mal. du coeur **43:** 920 (Oct.), 1950.

The authors present a study of the ventricular gradient in 50 cases of myocardial infarction with various localization. A_{QRS} was found to be normal in the majority (90 per cent) of the cases, while A_T had an abnormal direction in about the same percentage. The ventricular gradient (G) was found abnormal in 38 instances and the quotient G/A_{QRS} in 48 cases. There was no definite correlation of a certain localization of the infarct and alterations of the ventricular gradient. The authors conclude that the finding of an abnormal G suggests the presence of myocardial infarction even in the absence of a typical electrocardiographic pattern in the various leads.

PICK

Meneses Hoyos, J.: Electrocardiogram in the Agonal Heart. Arch. d. mal. du coeur **43:** 934 (Oct.), 1950.

In the experimental animal, in which electrocardiograms can be obtained 15 to 45 minutes after clinical death, the contour of the ventricular complexes is not typical for any agent producing death. The author reports electrocardiographic observations on a patient dying in uremia. The terminal stage to clinical death lasted seven minutes, and ventricular complexes were inscribed in the electrocardiogram for eight more minutes. In contrast to reported observations on sudden death with development of auricular fibrillation and abrupt ventricular standstill, slow death in man reveals the following sequence of electrocardiographic events: auricular fibrillation with progressive slowing of the ventricular rate, followed by a stage of intraventricular block, and finally diphasic and monophasic complexes of high voltage and extreme duration, termed by the author "agonal ventricular complexes."

PICK

Moll, A., Walka, K., and Korth, C.: The Value of Unipolar Extremity Leads for Clinical Electrocardiography. Arch. f. Kreislaufforsch. **16:** 125 (Oct.), 1950.

The authors present a critical survey of their experiences with "unipolar" limb lead and multiple chest leads in clinical electrocardiography. Unipolar limb leads are of value especially in the determination of electrical position of the heart under normal and abnormal conditions. Certain cases of left ventricular hypertrophy can be detected only with the help of these leads. In the recognition of right ventricular hypertropy, unipolar limb leads appear to be of lesser value than precordial leads. In cases of anterior infarction, the characteristic changes may be more distinct and may persist for a longer time in the unipolar limb leads compared with lead I and may remain the only evidence of remote infarction. The significance of various $T_1 < T_3$ types can be clarified by the use of unipolar limb leads. Lead aV_F is of importance in the recognition of posterior wall infarction, particularly in the healed stage. Unipolar limb leads may be helpful in the localization of atypical patterns of intraventricular conduction defect. Left bundle branch

block in indeterminate electrical position suggests the presence of an additional circumscribed myocardial lesion. Inversion of the T wave in a single unipolar limb lead may be normal and should be interpreted with caution.

PICK

Sodi-Pallares, D., Estandia, A., Soberón, J., and Rodriguez, M. I.: The Left Intraventricular Potential of the Human Heart. II. Criteria for Diagnosis of Incomplete Bundle Branch Block. Am. Heart J. **40**: 655 (Nov.), 1950.

The authors used the method of arterial cardiac catheterization to study the left cavity potentials of 25 patients of whom 13 had incomplete left bundle branch block. In the normal human heart, as in the dog's heart, the QRS complex inside the left ventricular cavity is of the QS type in the absence of any degree of left bundle branch block. If some degree of left bundle branch block exists, the left cavity complex is of the RS type, corresponding to the activation of the interventricular septum from right to left. Slurring in the beginning of the ascending limb of R in those leads which reflect the surface potential of the left ventricle (leads I, V_L, V_5 and V_6) suggests the existence of an initial positivity in the cavity of the left ventricle and therefore incomplete left bundle branch block. The changes in the morphology of the QRS are more important than the actual duration. The diagnosis can be made in the presence of QRS complexes with durations of less than 0.10 second. In two patients considered to have the Wolff-Parkinson-White syndrome, although the P-R intervals was 0.14 and 0.16 second respectively, bipolar trans-septal leads showed septal activation from right to left more consistent with the diagnosis of left bundle branch block.

HELLERSTEIN

Sodi-Pallares, D., Estandia, A., Soberón, J., and Rodriguez, M. I.: The Left Intraventricular Potential of the Human Heart. I. Method. Am. Heart J. **40**: 650 (Nov.), 1950.

The authors describe their technic of catheterizing the cavity of the human left ventricle to study the left intracavitary potential. Twenty-five patients studied included normals, hypertensives, and those with aortic insufficiency of syphilitic or rheumatic origin. The right radial artery was exposed under strict asepsis, and a ureteral catheter (Cournand) was introduced. The passage of the catheter through the aortic valve to the ventricular cavity was accomplished by gentle push and pull movements until it passed into the cavity. In 2 of the 25 patients, the catheter entered into the right coronary artery, producing an anginal crisis in one patient. The catheter was withdrawn in both cases to avert serious consequences. Ectopic beats were encountered particularly when the electrode was in contact with the higher portions of the interventricular septum. The one fatality in this series occurred in a patient with syphilitic aortitis and aortic insufficiency. There was no evidence of cardiac insufficiency noted in this case. The procedure was performed without incident. On the third day, without any premonitory signs, the patient suddenly died. Autopsy was not performed and the precise cause of death was not determined. In several patients both ventricular cavities were catheterized and transeptal bipolar leads were recorded to detect minimal grades of incomplete bundle branch block.

HELLERSTEIN

Herrmann, G. R., Hejtmancik, M. R., and Kopecky, J. W.: The Superiority of the Wilson Leads and the Value of Unipolar Limb and Precordial Derivations in Clinical Electrocardiography. Am. Heart J. **40**: 680 (Nov.), 1950.

The authors analyzed a series of 200 complete thirty-lead electrocardiographic studies in order to compare the findings over the precordium, using V, CR, CF, and CL leads. In all cases, the three standard leads and the three unipolar limb leads were taken. The clinical material was varied and included normal subjects and patients with hypertrophy, bundle branch block, infarct, cor pulmonale, and digitalis effect. The patterns displayed by the various precordial leads were a result of the potential differences between the exploring electrode and the extremity or terminal used as the indifferent electrode. Since the potential variations of the left arm and left leg are greatly affected by the electrical position of the heart, CL and CF leads show a great deal of variation. In patients with vertical electrical position, the high potentials of the left leg caused increased negativity in the CF leads. In electrically horizontal hearts, the high potentials of the left arm caused increased negativity in the CL leads. In the majority of patients, there was no significant difference in the various precordial leads. CF and CL leads showed the most variations from the other leads, depending on the electrical position of the heart. The V leads, in contrast to the other connections, were considered to be superior since no significant abnormalities were missed, and no false or exaggerated abnormalities were obtained by the V leads in this series. The authors proposed the designation W in honor of Dr. Frank N. Wilson, instead of V, which he and his associates applied to central terminal leads.

HELLERSTEIN

Lenzi, F., and Caniggia, A.: Electrocardiographic Changes Produced by Quinidine in the Normal and in the Injured Turtle Heart. Arch. d. mal. du coeur **43**: 1062 (Dec.), 1950.

The authors studied the effect of various intravenous doses of quinidine sulfate upon direct epicardial leads obtained from the exposed heart of turtles before and following cauterization. In the

intact heart, marked slowing was observed terminating, with massive doses, in complete, fatal cardiac arrest. The P waves become initially larger and notched and later diphasic. This was considered to indicate interatrial dissociation. P-R and Q-T intervals and QRS duration showed prolongation proportional to the dose of quinidine used. The time of repolarization was prolonged, as evidenced by depression of S-T and flattening to inversion of the T waves, especially after large doses of the drug.

S-T elevations and tall upright T waves produced by cauterization disappeared following administration of quinidine. The latter observation suggests an action of quinidine upon the subendocardial layer of the myocardium, opposite to the effect of subepicardial injury.

PICK

Binder, M. J., Gunderson, H. J., Cannon, J., and Rosove, L.: Electrocardiographic Changes Associated with Allergic Reactions to Penicillin. Am. Heart J. **40**: 940 (Dec.), 1950.

The authors observed transient T wave inversion in 3 patients who developed severe allergic reactions after penicillin in oil and beeswax or penicillin in oil. There were no complaints referable to the cardiovascular system, and no clinical evidence of pericarditis or myocarditis. Electrocardiographic abnormalities were not found in an additional 25 patients with mild allergic reactions during penicillin therapy. This suggests that electrocardiographic changes occur only with the most severe reactions. The T wave changes are not specific for penicillin allergy, since they resemble those previously reported in other allergic reactions.

HELLERSTEIN

Kuo, P. T., and Vander Veer, J. B.: Electrocardiographic Changes in Pulmonary Embolism with Special Reference to an Early and Transient Shift of the Electrical Axis of the Heart. Am. Heart J. **40**: 825 (Dec.), 1950.

The authors report a series of 7 cases of proved pulmonary embolism studied with serial electrocardiograms. In 3 cases with minor pulmonary emboli, the electrocardiogram showed sinus tachycardia, prominent Q and inverted T wave in lead III, prominent S wave in aV_L, with little or no S wave in lead I, a generalized lowering of all waves in all leads, and some shift of the transitional region to the left. This pattern appeared almost immediately following pulmonary embolism and often returned to nearly normal within a few hours. Two patients showed the characteristic pattern of McGinn and White. One patient showed the patterns of acute cor pulmonale and the axis shift of minor pulmonary embolism. One patient was in severe shock after massive pulmonary embolism and showed multiple electrocardiographic changes: transient auricular fibrillation, acute cor pulmonale pattern, delayed right intraventricular conduction, and T wave and S-T changes in the chest leads. When the right ventricle dilates as a result of pulmonary embolism, the heart is rotated on its anteroposterior axis, and assumes a relatively vertical position in the chest, accompanied by clockwise rotation on the longitudinal axis and posterolateral displacement of the left ventricle. The production of a Q wave in lead III in all 7 patients was favored by these positional changes and by the circulatory disturbances of the myocardium which decreases the left leg potentials more than that of the left arm.

HELLERSTEIN

Slapak, L., and Partilla, H.: The Diagnosis of Posterior Wall Infarction and of Aneurysm of the Posterior Wall in the Electrocardiogram. Acta med. Scandinav. **139**: 42 (Dec.), 1950.

Electrocardiographic changes indicative of posterior wall infarction can be seen in special bipolar chest leads, when one electrode is placed in the posterior axillary line and the other at various points in the second left intercostal space between left sternal border and anterior axillary line. By this method the authors were able to demonstrate the presence of recent or healed posterior wall infarction in 17 cases, in which the diagnosis could not be made from the conventional leads or from dorsal leads according to the method of Nehb, probably due to infarction of only a small area of the posterior wall. In 2 cases of posterior wall aneurysm, proved at autopsy, the leads recommended by the authors showed the persistent elevation of the S-T segment considered to be characteristic of ventricular aneurysm due to infarction.

PICK

Stroeder, N.: Electrocardiographic and Kymographic Investigations in Standing Position before and following Application of Hydrated Ergot Alkaloids under Consideration of Leukocyte and Blood Sugar Levels. Cardiologia **17**: 127, 1950.

The authors report comparative electrocardiographic and kymographic studies on the effect of various sympatholytic agents of the ergot group (CCK, DHE 45, DHO 180) in 70 patients with neurovegetative lability. The ST-T in the electrocardiogram was abnormal in supine position in 35 instances and became normal or improved following injection of the sympatholytic agent in 23 instances. Orthostatic variations of the electrocardiogram were seen in 60 cases and were improved by the various drugs in 57 instances. The occurrence of ST-T changes and their regression could be correlated in all instances with the degree of tachycardia and the effect of the sympathicolytic action upon the heart rate. Patients with tendency to orthostatic collapse associated with tachycardia developed definite electrocardiographic changes, which were absent in cases with bradycardic (vasovagal) type of syncope. Following application of DHE, enlargement of

the heart shadow was seen to occur in 18 cases. The increased heart size is ascribed by the author, on the basis of kymographic studies, to an increase of the residual blood volume in the ventricles (regulative dilatation).

PICK

Unghvary, L., and Schulz, A.: Changes of the Electrocardiogram in the Chest Leads Corresponding to Changes of the Position of the Electrical Axis. Cardiologia **17**: 295, 1950.

The senior author, in 1939, attempted to explain changes of the ventricular complexes in the semidirect chest leads by changes of the mean electrical axis in space. In the present paper the authors report experiments which were performed in order to prove this fact. The heart of a dog was exposed and four twines were attached to the apical area. Four ends of these twines were led between the ribs, outside of the chest anteriorly, posteriorly, on the right and on the left. The chest wall was closed. With the aid of the twines the heart is rotated to the left or right or moved anteriorly or posteriorly. The electrocardiograms obtained in the CF leads showed the changes one would expect from the altered position of the electrical axis.

SCHERF

Papp, C., and Smith, K. S.: Electrocardiographic Patterns in Slight Coronary Attacks. Brit. Heart J. **13**: 17, 1951.

The term "slight coronary attack" is applied to an attack of precordial pain, usually responsive to a single dose of morphine and accompanied by electrocardiographic signs of infarction, but without shock or other signs of myocardial necrosis. However, 5 of the 33 instances reported had abnormal white blood cell counts and sedimentation rates. The electrocardiographic pattern in 16 of 17 anteroseptal infarcts, in 5 of 7 anterolateral infarcts and in 5 of 6 posterior infarctions reverted to normal. There were 2 apical and 3 posterolateral infarctions. Seventeen patients had angina pectoris preceding and 6 manifested the anginal syndrome following infarction. Abnormality of the R-T or T wave patterns was present in all tracings. Abnormal Q waves were present in only 6 patients. The lesions are regarded as small intramural or patchy subendocardial infarctions. The immediate prognosis is good in these patients.

Because of the good prognosis, rest in bed is shortened to two weeks. These patients are encouraged to move and sit up in bed. Anticoagulant therapy is not indicated in these patients.

SOLOFF

Taran, L. M., and Szilagyi, N.: The Q-T Interval in Rheumatic Disease in Children. Brit. Heart J. **13**: 10, 1951.

The authors report upon the Q-T interval of the electrocardiograms of 140 rheumatic children, 6 to 16 years of age. Those who had crude disorders in rhythm, pericardial effusion, acidosis, hypocalcemia or drug therapy such as digitalis, mercurials, salicylates or quinidine, were excluded. Of 123 who were observed during a single period, the Q-T segment shortened in 33, lengthened in 51 and remained unchanged in 39 of whom 13 were normal. Of 17 who were observed for several periods the Q-T shortened in 9 and was lengthened in 8 patients.

In the first group there was a close association between the changing duration of the Q-T interval and the clinical evidence of carditis. The second group demonstrates that the longer the time during which the Q-T is prolonged, the more extensive is the cardiac damage.

SOLOFF

HYPERTENSION

Kositchek, R. J., and Rabwin, M. H.: Pheochromocytoma Successfully Removed with the Aid of Piperoxan (Benodaine) Hydrochloride. J.A.M.A., **144**: 826 (Nov. 4), 1950.

A white man, 37 years old, suddenly manifested attacks suggestive of pheochromocytoma, but perirenal air insufflation revealed no evidence of a tumor. The histamine and piperoxan tests substantiated the clinical impression of pheochromocytoma. There was no clue as to where the tumor might be located. Following the administration of adrenal cortex extract to combat possible adrenal insufficiency, the patient was operated upon. Blood pressure was 130/60 when the patient was brought to the operating room, but as a result of manipulation associated with the administration of spinal anesthesia the pressure rose to 260/150. Thiopental sodium was then administered intravenously, and at the beginning of the operation the pressure dropped to 160/120. The tumor was found in the left adrenal gland and palpated. At this time the systolic blood pressure rose to 350 mm. Hg., which was the top of the manometer; diastolic pressure was 200 mm. Hg. At this point piperoxan hydrochloride was injected intravenously and the blood pressure came down to 220/120. The extirpation of the tumor was accomplished while the drug was being slowly injected to maintain the lowered blood pressure. This was stopped and epinephrine, ephedrine and paredrine with oxygen were administered as the blood pressure dropped to zero when the tumor was removed. Six months later the patient was in excellent health and maintaining a normal blood pressure. At that time the piperoxan test had no effect on the blood pressure.

KITCHELL

Barell, G.: Concerning the Time of Onset of Blood Pressure Elevation and the Significance of the Adrenals in Experimental Arterial Hypertension. Helvet. med. acta **6**: 599 (Dec.), 1950.

The author describes a method for production of persistent hypertension in rats by compression of one kidney following extirpation of the other. The blood pressure was determined in the tail of the animal by an indirect plethysmographic method. Normal pressure values were found to vary between 90 and 130 mm Hg. Only repeated readings over this value were considered to indicate hypertension. Elevation of the blood pressure was observed two to seven hours following the operation and could be maintained over a considerable period of time, extending in some experiments over more than two weeks. Adrenalectomy preceding the operation did not alter the time of onset and the duration of the pressure elevation.

PICK

Goldenberg, M., Aranow, H., Smith, A., and Faber, M.: Pheochromocytoma and Essential Hypertensive Vascular Disease. Arch. Int. Med. **86:** 823 (Dec.), 1950.

Eighteen patients who had pheochromocytoma with persistent hypertension and 4 patients who had pheochromocytoma with paroxysmal hypertension were subjected to clinical analysis. Fifteen of the tumors were analyzed by chemical means. Total epinephrine and/or Arterenol content and the ratio of epinephrine to Arterenol did not differ essentially in the two groups.

In the patients who had pheochromocytoma with persistent hypertension the following correlation could be established: When the tumor contains epinephrine predominantly, or a large amount of Arterenol, the picture is characterized by hypertension, tachycardia, hyperhidrosis, hypermetabolism and, frequently, hyperglycemia. Tests with piperoxan hydrochloride give positive reactions. When the tumor is small and contains for practical purposes Arterenol only, the syndrome of essential hypertensive vascular disease is closely mimicked. An increase in basal metabolic rate may be present and the test with piperoxan hydrochloride gives a positive reaction.

This correlation is limited in that, in certain stages of the disease, no evidence of increased circulating catechols (epinephrine and Arterenol) can be obtained; i.e., hypertension may be present, with normal basal metabolic rates, normal pulse rates, lack of hyperglycemia and negative piperoxan reactions. Intermittent, as well as continuous, secretion of the catechols by the tumor may lead to persistent hypertension.

Hypertension persisted for varying periods in 7 of 12 patients whose chromaffin tumors were operatively excised, although all other clinical signs regressed promptly. This corroborates the view that excessive amounts of circulating catechols need not be constantly present to maintain the elevation in blood pressure initially produced by them ("secondary hypertension"). The possible relation of "secondary hypertension" in pheochromocytoma to essential hypertensive vascular disease is discussed.

BERNSTEIN

Harris, J. S., Sealy, W. C., and deMaria, W.: Hypertension and Renal Dynamics in Aortic Coarctation. Am. J. Med. **9:** 734 (Dec.), 1950.

The authors review critically the controversial literature concerning the genesis of the blood pressure changes in coarctation of the aorta. In the upper extremities hypertension is the rule. It is felt that, although mechanical obstruction may contribute to the hypertension, some other mechanism appears to contribute to that hypertension either by increasing peripheral resistance, or by preventing the full action of compensatory mechanisms designed to lower the blood pressure. Because of the evidence indicating inadequacy of the mechanical theory and because of lack of direct evidence implicating the kidneys, the investigators studied further the relation between the hypertension and the kidneys by observation of the changes in renal dynamics before and at intervals following the surgical relief of the coarctation in 4 patients. No correlation was found between the blood pressure changes and the renal dynamics before and after operation. The authors conclude that other mechanisms, besides the increased resistance imposed by the constriction and collaterals, are necessary to explain the hypertension of aortic coarctation. These mechanisms apparently do not involve renal ischemia.

HARRIS

Keith, N. M., and Wagener, H. P.: Recession of Neuroretinopathy during the Course of Malignant Hypertension. Arch. Int. Med. **87:** 25 (Jan.), 1951.

The papilledema of malignant hypertension has been shown to recede in a series of 15 patients in whom the cause of this objective improvement is still unknown. The observation of this recession leads to a better understanding of the future course of the disease and to the recognition that life expectancy is usually increased when such recession occurs. Studies of the retina in this series of 15 patients have brought out several interesting facts. In 3 patients papilledema developed in the presence of considerable generalized and focal constriction of the arterioles, but in the absence of definite evidence of generalized arteriolosclerosis. In 2 of these patients, retinopathy was associated with the papilledema. The lesions in the fundi could be considered then to represent an acute angiospastic or hypertensive episode. A fairly rapid recession of the papilledema, or of the papilledema and retinopathy if present, would suggest a relatively favorable prognosis. This course of events was observed in 2 of the cases. The patients lived 68 and 138 months, respectively, after papilledema was discovered. In the

third case, however, the papilledema and retinopathy did not recede rapidly and death occurred 20 months after papilledema was observed.

Delay in recession of the retinopathy after recession of the papilledema occurred at times and was difficult to explain. Facts suggest that the presence of arteriolosclerosis, even of considerable degree, does not militate necessarily against the chances of recession of retinopathy and papilledema and for long survival in individual cases. The authors' observations are similar to those in cases in which recession of papilledema followed a variety of beneficial therapeutic measures.

BERNSTEIN

PATHOLOGIC PHYSIOLOGY

Cassels, D. E., Morse, M., and Adams, W. E.: Effect of the Patent Ductus Arteriosus on the Pulmonary Blood Flow, Blood Volume, Heart Rate, Blood Pressure, Arterial Blood Gases and pH. Pediatrics **6**: 557 (Oct.), 1950.

The pulmonary blood flow was found to diminish from 19.6 to 61.8 per cent by the Fick method in 12 cases of a patent ductus arteriosus following ligation. Using the dye method, it was found that of 13 cases, 10 had smaller plasma volumes and 9 had smaller blood volumes two to three weeks postoperatively. Closure of the ductus was followed by an average diminution of heart rate of 11 beats per minute in the sitting position, and 14 beats per minute in the standing position. In the majority of cases the diastolic pressure increased and the systolic pressure decreased after ligation. However, in 2 patients, the diastolic pressure was lower than the preligation pressure. After ligation, the average decrease in systolic pressure was 5.7 mm. of mercury, and the average increase in diastolic pressure was 5.4 mm., thus producing an average fall in pulse pressure of 11.1 mm. In 23 cases the average preoperative arterial oxygen saturation was 95.4 per cent, which was similar to the average of 95.7 per cent in 39 normal control children. However, 3 cases had low values of 92.3, 87.5 and 89.8 per cent. Two to three weeks after closure of the ductus in 20 cases, 17 had lower oxygen saturation levels than the preoperative value.

The authors hypothesize that cases with low arterial oxygen saturation preoperatively may be due to impaired diffusion due to vascular changes as a result of excessive pulmonary blood flow.

MARGOLIES

Weinberg, S. J., Goodman, J. R., and Bushard, M. C.: Alterations in Renal Function, Including Hematuria, in Man During Intracranial Air Studies. Arch. Int. Med. **86**: 857 (Dec.), 1950.

In 10 male patients undergoing controlled diuresis, ventriculography and pneumoencephalography was accompanied with antidiuresis, reduction in output of urinary chloride and nitrogen and, in several instances, electrocardiographic changes. In the majority of these studies red blood cells appeared in the urine during antidiuresis, together with white blood cells, round epithelial cells and, in one case, albumin.

The evidence supports the hypothesis that the urinary fluctuations in chloride, urea and volume are independent, each constituent having its own control mechanism.

The evidence favoring a central regulating mechanism responsible for anuria and nephritis is discussed.

BERNSTEIN

Zimmerman, H. A.: Left Ventricular Pressures in Patients with Aortic Insufficiency Studied by Intracardiac Catheterization. J. Clin. Investigation **29**: 1601 (Dec.), 1950.

In 10 subjects with aortic insufficiency the left ventricle was catheterized via the radial artery. The diastolic pressure in the 3 subjects without cardiac failure was normal (average 1.3 mm. of mercury). In the 7 patients who had congestive failure the left ventricular diastolic pressure ranged between 15 and 39 mm., with an average of 25 mm. This finding is in keeping with the Starling hypothesis, and with the finding that in failure a large amount of residual blood remains in the ventricles after systole.

WAIFE

Gürson, C. T.: Alterations of the Circulation in Toxemia. Helvet. pediat. acta **6**: 489 (Dec.), 1950.

Forty-nine cases of infantile toxemia accompanied by dehydration and acidosis were studied for alterations of blood pressure and size of the heart, and by serial electrocardiograms. In 81.5 per cent of the cases the blood pressure was found to be elevated, in 16 per cent normal and in 4.7 per cent lower than normal. Abnormalities of the electrocardiogram were found in 79.5 per cent and consisted in inversion of T, depression of S-T and prolongation of Q-T, the latter in more than half of the cases. Disturbances of conduction were seen less frequently. X-ray examinations revealed diminution of the heart shadow as described previously in cases of toxemia. Both electrocardiograms and roentgenologic findings, which had been abnormal, became normal, with clinical improvement and normalization of the blood pressure. The author concludes that toxemia is a disease associated with increase of blood pressure and imposing a marked strain upon the circulatory system.

PICK

Van Noate, H. F.: Right and Left Atrial Pressures in Successive Stages of Oligemic and Normovolemic Shock. Proc. Soc. Exper. Biol. & Med. **76**: 155 (Jan.), 1951.

It was the purpose of this investigation to study pressure relations by simultaneous registration of right and left atrial pressures, for it has never been proved that the beats of the two ventricles are coordinated so perfectly during oligemic and normovolemic shock that changes in filling pressure for the right ventricle are automatically accompanied by similar quantitative or even directional changes on the left side.

The results indicate that myocardial depression can occur during the circulatory failure which develops after prolonged hemorrhagic hypotension and subsequent reinfusion of the withdrawn blood. The myocardial failure may affect either the left or right ventricle dominantly.

MINTZ

Kisch, B.: The Mechanics of Flutter and Fibrillation. A Short Review of a Century of Studies. Cardiologia **17**: 244, 1950.

Of the four theories on the mechanism of flutter and fibrillation none has been convincingly proved or disproved. The first theory assumes a polyfocal origin of the impulse, the second a single rapid focus, a third implies a circulating wave within the fibrillating heart and the last theory supposes fractionated multiple contractions of the heart.

The presence of two independent rapid heart rhythms was demonstrated by the author by direct epicardial leads taken from the fibrillating ventricle of the duck. The mechanical inefficiency of the fibrillating ventricle seems to depend primarily on the anisorhythmic action of the two foci and not upon the high degree of tachycardia. This can be shown in the bird heart where the fibrillation rate of the ventricles may be less than the regular rate, which may reach 500 or more per minute.

PICK

Biegen, E., and Aas, K.: Renal Blood Flow and Glomerular Filtration Rate in Patients with Valvular Heart Lesions. Acta med. Scandinav. **138**: 391, 1950.

Renal plasma flow and glomerular filtration rate were studied by means of the sodium para-aminohippurate and inulin technics in 8 normal individuals, 37 patients with valvular cardiac disease and 3 other patients with heart block, coarctation of the aorta and pericardial constriction. Decreased renal blood flow, decreased glomerular filtration rate and increased filtration fraction were found in nearly all of the patients with heart disease. Moreover, these abnormalities were present not only with right cardiac failure, but even in patients with the slightest left cardiac failure, that is, dyspnea on exertion. These results are considered evidence against the belief that decreased renal function is of major importance in pathogenesis of cardiac edema.

Hypoxemia was induced in several of the patients by having them inhale 9.5 per cent oxygen in nitrogen. This produced an increased renal blood flow, averaging 16 per cent, and a slight increase in glomerular filtration rate, averaging 3 per cent, in all of the patients with valvular lesions except those with aortic stenosis. This result was interpreted as evidence that hypoxemia in itself is not the cause of reduction in the renal blood flow as it occurs in congestive heart failure.

Patients with aortic stenosis did not show an increase in renal blood flow in response to induced hypoxemia. The reason for this is not clear, but it is suggested that these patients not only have a low pulse pressure initially, but that they are unable to increase the pulse pressure in response to this special need. It is mentioned that this inability to undergo a vascular reaction may also lead to insufficient cerebral and coronary blood flow during stress leading, therefore, to the syncopal attacks which are so common in aortic stenosis.

ROSENBAUM

PATHOLOGY

Prior, J. T., and Wyatt, T. C.: Endocardial Fibro-Elastosis. Am. J. Path. **26**: 969 (Nov.), 1950.

The authors review their clinical and pathologic findings in 8 cases of endocardial fibro-elastosis. This congenital cardiac abnormality consists of marked cardiac enlargement in infancy, contributed entirely by hypertrophy and dilatation of the left ventricle. It is associated with grey, opaque thickening of the endocardium of the left side of the heart, sometimes of the left auricle, always of the left ventricle.

In 3 of the 8 cases, there was associated aortic and mitral valvular thickening resulting in stenosis. No vegetations were noted and microscopy revealed an absence of inflammatory reaction both in the valvular and the diffusely thickened mural endocardium. The thickening was due to a marked hyperplasia of elastica. Collagen was slightly increased. The myocardium showed degenerative changes only in the papillary muscles and at the subendocardial junction. Here glycogen was deposited, but in no other portion of the hypertrophied myocardium.

These infants were apparently normal at birth. The oldest was 9 months, the average age, 4 months. The sudden onset of symptoms, most commonly cyanosis, and the short duration of life thereafter, were striking clinical features. Murmurs were heard in one case. No case was diagnosed ante mortem. No electrocardiographic study was made. A left axis preponderance ought to exist in every case on the basis of the pathologic changes. Death was caused in all cases by acute congestive failure. The authors discuss the possible causes of this failure and advance an interesting theory, namely, that the thick, rigid endocardium may act in a manner analogous to that of chronic constrictive pericarditis, limiting both the

diastolic filling and the systolic expulsion of blood in the left ventricle.

GOULEY

Hodges, H. H., and Gilmour, M. T.: Myocardial Contusion. The Report of a Fatal Case with Autopsy. Ann. Int. Med. **34:** 248 (Jan.), 1951.

A 59 year old male, injured in an automobile accident, suffered fractures of the right clavicle, the upper six ribs on the left side and the upper five ribs on the right side. Approximately two days after the accident, he developed evidences of left ventricular failure associated with a sinus tachycardia and minor T wave alterations in the electrocardiogram. In spite of digitalization, his condition did not improve and on the third day after the accident, the electrocardiogram revealed the presence of auricular fibrillation with a rapid ventricular rate. His condition thereafter became progressively more grave in spite of treatment with digitalis, quinidine, aminophylline, Coramine and mercurial diuretics. Death occurred on the sixth day after the accident and at autopsy the significant findings consisted of microscopic foci of necrosis distributed irregularly throughout the wall of the left ventricle. The foci of necrosis were characterized by partial or complete loss of cross striation, collapse of sarcoplasm, disintegration of muscle fibers, degenerative changes and loss of nuclei. Some of the foci of necrosis were accompanied by hemorrhages, but no inflammatory reaction was noticeable. Similar changes were entirely absent in the wall of the right ventricle.

WENDKOS

Jervell, O.: Pulmonary Sclerosis. Acta med. Scandinav. **138:** 430, 1950.

Four cases of chronic cor pulmonale are described. One is ascribed to a thoracic deformity due to a thoracoplasty, another to asthmatic bronchitis with pulmonary emphysema, the third to pulmonary endarteritis probably of syphilitic origin, and the fourth case is designated a true, so-called primary, pulmonary sclerosis. The diagnosis of pulmonary sclerosis is difficult since insufficiency of the right ventricle with edema, right axis deviation in the electrocardiogram, and prominence and pulsation of the pulmonary conus must all be regarded simply as signs of pulmonary hypertension. So-called primary pulmonary sclerosis presents, on the whole, the same clinical signs and the diagnosis arrived at is not infrequently mitral stenosis. Sclerosis of the pulmonary artery occurs in elderly subjects, mitral stenosis, chronic lung diseases, and in conditions which seem to have a constantly elevated pulmonary pressure of unknown origin. It is considered that infectious or toxic influences combined with pulmonary hypertension are the cause of the degenerative changes in the vessels of young patients with pulmonary sclerosis. It is suggested that the term Averza's disease should be restricted to those cases of chronic cor pulmonale in which severe cyanosis is the most prominent symptom. The severe cyanosis in such cases is considered due to several factors including polycythemia, hypoventilation, pulmonary emphysema, and pathologic or functional changes in the small vessels and capillaries of the lung.

ROSENBAUM

Thomas, A. J.: Right Ventricular Hypertrophy in the Pneumoconiosis of Coalminers. Brit. Heart J. **13:** 1, 1951.

This report is based upon a study of 50 unselected hearts from individuals with pneumoconiosis and of 146 electrocardiograms from 44 normals, 41 with simple pneumoconiosis, 24 with pneumoconiosis complicated by massive shadows in the lungs and 25 with more advanced pulmonary changes. Although the mean ratio of ventricular weight to body weight was slightly above normal, right ventricular preponderance was present even in the small hearts, of which there were many. The musculature of the outflow tract of the right ventricle shows the earliest enlargement. The electrocardiographic study indicated that increasing lung disease produces decreasing voltage of R and increasing voltage of S in V_6. An R′ of 4 mm. or more in the third intercostal space above V_2 is regarded as helpful in the diagnosis of right ventricular hypertrophy.

SOLOFF

PHARMACOLOGY

Gimbel, N. S., Riegel, C., and Glen, W. W. L.: Metabolic and Cardiovascular Studies of Prolonged Intravenous Administration of Human Serum Albumin. J. Clin. Investigation **29:** 998 (Aug.), 1950.

The authors present detailed metabolic studies on the administration of human salt-poor albumin to 3 normal subjects. When human albumin, supplemented with *dl*-acetyltryptophane, was infused, large amounts of albumin accumulated in the plasma, interstitial fluid, and lymph. Albuminuria may develop. As larger quantities of albumin accumulate increasing amounts are catabolized.

When albumin was taken by mouth, quantities less than 75 Gm. were insufficient to maintain nitrogen equilibrium. One subject on 75 Gm. of serum albumin intravenously per day developed congestive heart failure as indicated by an enlarged tender liver, increased plasma volume, cardiomegaly, left axis deviation of the electrocardiogram, and a 20 per cent decrease in cardiac output as determined by ballistocardiogram. The marked symptoms of congestive failure regressed within five days after cessation of albumin effusion. The authors believe that considerable care should be exercised in administering albumin to patients with low circulatory reserve and to those who have no albumin deficiency.

The danger of circulatory overloading hampers the usefulness of albumin as a nutritional supplement.

WAIFE

Leach, E. M., and Gibson, S.: Auricular Flutter in Infancy. Am. J. Dis. Child. **80:** 606 (Oct.), 1950.

The authors report a 6 month old boy with auricular flutter and a varying 3:1 to 5:1 auriculoventricular block. The electrocardiogram also showed a right heart strain which was thought to be compatible with congenital heart disease. The electrocardiogram showed peaked P waves in leads II and III with right heart strain. Digitalis was tried, but the drug was poorly tolerated. Quinidine sulfate, 36 mg. every two hours for five doses, as well as a small daily dose of digitalis (12 mg.) was administered. The auricular flutter changed to impure flutter, then to auricular fibrillation and finally to a normal sinus rhythm. The quinidine was reduced to 18 mg. every six hours and the auricular flutter returned. The dose of quinidine was increased, but the child became lethargic so quinidine was stopped. In two months the child had a normal sinus rhythm, but cardiac enlargement was still present. It was felt that the lesion was probably an auricular septal defect.

Previous to this case, there have been only 12 cases of auricular flutter in infancy reported; 6 occurred in infants under the age of 6 months.

MARGOLIES

Mackey, W. A.: Intra-arterial Histamine in Treatment of Claudication. Brit. M. J. 4688: 1086 (Nov.), 1950.

The vascular effects of weekly intra-arterial injections of histamine were studied in 14 cases of arteriosclerosis obliterans. In each instance 500 cc. of normal saline containing 2 mg. of histamine acid phosphate were delivered under pressure into the femoral artery over a period of 30 to 45 minutes.

The reactions to the medication consisted of an immediate bright flushing in the thigh down to the knee, an increased skin temperature over this area, and a striking but transient increase in oscillometric readings at the level of the calf. After several treatments there was a tendency for the flushing to extend further down the leg and in some cases to reach the toes.

After a course of therapy, consisting of ten infusions, walking improved and rest pain diminished in 9 patients, while in 5 no change was observed. In no case did the treatment produce any obvious harm. It was pointed out by the author that in general the improvement achieved was essentially subjective and clinical. In only a few cases was there any permanent change in the oscillometric readings.

ABRAMSON

Carey, R. A., Harvey, A. M., and Howard, J. E.: The Effect of Adrenocorticotropic Hormone (ACTH) and Cortisone on the Course of Disseminated Lupus Erythematosus and Periarteritis Nodosa. Bull. Johns Hopkins Hosp. **87:** 387 (Nov.), 1950.

The authors treated 12 cases of disseminated lupus erythematosus, 5 patients who had extensive cutaneous lesions without pronounced systemic manifestations, and 1 case of periarteritis nodosa with either ACTH or cortisone. No uniform treatment schedule was followed.

In each of the 12 cases of disseminated lupus, there was an immediate and dramatic response. Within 24 hours the joint pains disappeared and the temperature became normal. In 4 cases there has been no clinical recurrence with remissions lasting from 3 months to 11 months. Five cases have had relapses from seven days to four months after treatment. Two of these cases received further therapy, 1 relapsed again after seven days and the others went into complete remission for six months. Two cases died, 1 of a bacterial infection and the other of renal insufficiency.

In the five cases having predominant cutaneous lesions, the diagnosis of lupus erythematosus was confirmed by biopsy of the skin before therapy was instituted. Two patients having lesions of eight months duration relapsed shortly after the termination of therapy. Of the 3 patients with lesions of recent origin, one relapsed two weeks after therapy and 2 had remissions.

A single case of periarteritis nodosa treated with ACTH is presented in detail with serial muscle biopsies showing healing of the lesions.

MARGOLIES

Howard, J. P., Levy, L., and Adriani, J.: The Effects of Epinephrine and Ephedrine Administered Intrathecally upon Cardiac Automaticity During Cyclopropane Anesthesia. Anesthesiology **11:** 694 (Nov.), 1950.

Vasoconstrictor drugs are often administered intrathecally to prolong the duration of spinal anesthesia. Since cyclopropane increases the irritability of the heart and since intravenous epinephrine behaves similarly the authors studied the effect of intrathecal vasoconstrictors on cardiac rate and rhythm during cyclopropane anestheisa in dogs. Continuous electrocardiographic observation for one hour after administration revealed no changes in rhythm. After one hour sufficient epinephrine was still present in cerebrospinal fluid to cause severe cardiac arrythmias when withdrawn and administered intravenously.

WAIFE

Rose, O. A., Lhowe, J., and Batterman, R. C.: Mercumatilin (Cumertilin): A New Mercurial Diuretic for the Treatment of Congestive Heart Failure. Am. Heart J. **40:** 779 (Nov.), 1950.

The authors compared Mercumatilin (Cumertilin) and Mercuhydrin as to predictability of diu-

retic response, degree of diuresis, safety and local tolerance. A total of 28 patients with organic heart disease and varying degree of congestive heart failure were studied. The diuretics were administered intramuscularly in the dosage of 2 cc. in the morning. On the basis of predictability of obtaining a satisfactory diuresis (loss of 3 pounds of edema fluid over a period of 48 hours after injection) Mercumatilin was as effective as Mercuhydrin. The degree of diuresis for both drugs was similar. The omission of ammonium chloride did not materially alter the predictability of response of Mercumatilin. This was not true of Mercuhydrin. Neither produced significant local reactions or evidence of systemic toxicity. Mercumatilin is considered to be a safe and effective mercurial diuretic for intramuscular injection.

HELLERSTEIN

Siems, L. L., and Rottenstein, H. S.: The Locus of the Peripheral Vasodilator Action of Ethyl Alcohol, Tetraethyl Ammonium and Priscoline. Am. J. M. Sc. **220:** 649 (Dec.), 1950.

This study was conducted in an effort to localize the site of action of vasoactive drugs. The technic employed was a cross perfusion preparation using two dogs with the carotid artery of each animal connected to the femoral artery of the other; and the external jugular vein and femoral vein of each animal connected in the same way. By this means each animal supplied arterial blood to one hind leg of the other dog and no blood from that leg was able to flow into the general circulation of that dog. Various drugs were injected intravenously into one dog. The effect of the drug upon blood flow in its own perfused leg must have been mediated by the intact nerve supply. The local action of the drug was evaluated by means of its effect upon blood flow in the perfused leg of the other dog into whose general circulation the drug did not appear. Bubble flowmeters were employed to measure changes in peripheral resistance, the perfusion pressure being maintained constant.

The drugs employed in this study were (a) Priscoline, which had only a local peripheral vasodilating effect; (b) alcohol, which appeared to be effective through vasomotor nerve supply with no local action; and (c) tetraethylammonium chloride, which had both the vasomotor nerve mediation of vasodilation, possibly through blockade of vasoconstrictor nerves at the ganglions, and a locally effective vasodilator component which is not explained.

SHUMAN

Bernstein, L., O'Neill, P. B., Bernstein, A., and Hoffman, W. S.: Pergastric Intestinal Perfusion for Uremia. J. Lab. & Clin. Med. **36:** 849 (Dec.), 1950.

The authors perfused the whole intestine in 9 preterminal uremic subjects by passage of fluid through a double lumen gastric tube and the collection of the intestinal perfusate at the anal canal with the help of a rectal tube. Suction at the cardia served to prevent overdistension of the stomach and vomiting.

Urea and nonprotein nitrogen were well excreted in the intestinal perfusate, but only slightly excreted in the gastric perfusate. Serum nonprotein nitrogen levels dropped an average of 59 mg. per 100 cc. The calculated urea clearance of the perfusion was as high as 21 cc. per minute. The excretion of creatinine was much less significant and that of phosphate and phenols was not appreciable. Two of the 9 subjects were markedly improved clinically and their deaths from uremia were delayed.

Losses of potassium up to 12.7 Gm. occurred even when the concentration of potassium in the perfusing fluid was twice as high as that of the serum.

Retention of water, sodium, chloride and bicarbonate occurred in all subjects. This retention was beneficial in the dehydrated patients, but in the others these increases were harmful. It would be more desirable to use lower concentrations of sodium and chloride.

The optimal rate of perfusion was about 2.5 liters per hour. At this rate the urea excretion was greatest and the absorption of sodium and chloride as well as the loss of potassium was relatively low.

The authors found that short perfusions of not more than six to eight hours were safer than longer ones. The perfusion may be repeated after serum analyses and appropriate adjustments of the electrolyte composition of the perfusing fluid are made.

MINTZ

Nalefski, L. A., and Brown, C. F. G.: Action of Atropine on the Cardiovascular System in Normal Persons. Arch. Int. Med. **86:** 898 (Dec.), 1950.

Atropine has varying effects on the heart rate, depending on the age of the subject. The younger groups showed a sharper increase in rate after atropine administration, with a more rapid return to normal, than the older groups. If the degree of vagal tone can be measured by the changes in heart rate after atropine administration, then these results indicate that vagal tone is greatest in childhood and gradually decreases through the succeeding decades, except for the relative differences observed between the ages of 40 to 60.

The subjects showed a great variability in blood pressure changes on atropine administration. The same person, however, displayed a characteristic reaction when the test was repeated on different occasions. The subjects below the age of 20 and over the age of 55 showed less change in blood pressure reactions after the administration of atropine. The reactions in those from 20 to 55 were brisk, varying and unpredictable. The diastolic blood pressure usually rose after atropine was given and became more elevated in older persons.

Measuring the reactions of the vegetative system to atropine and observing a greater individual variability in the threshold of nerve control among normal persons in the age groups showing the greatest incidence of coronary heart disease has led the authors to believe that atropine sulfate should play a prominent role in the treatment of coronary thrombosis.

BERNSTEIN

SURGERY IN HEART AND VASCULAR SYSTEM

Murray, G.: Treatment of Mitral Valve Stenosis by Resection and Replacement of Valve under Direct Vision. Arch. Surg. **61:** 903 (Nov.), 1950.

The author describes a method for resection of a portion of a stenosed mitral valve and for insertion of a valve to prevent regurgitation. This procedure has given fairly satisfactory results in a few patients. The operation is done though a cannula and may be done partly under direct vision through a cardioscope. It may be useful in the treatment of this lesion until such time as a dry heart can be safely produced. Postoperative heparinization was used. All the patients operated on were in the later stages of mitral stenosis.

BECK

Poppen, J. L.: Ligation of the Internal Carotid Artery in the Neck. Prevention of Certain Complications. J. Neurosurgery **7:** 532 (Nov.), 1950.

The author discusses the indications for ligation of the internal carotid artery in the neck, both emergency and elective. He advises this procedure only as a last resort. He describes the several pitfalls and particularly emphasizes the competence of the collateral circulation. He discusses ligation of the internal carotid versus the common carotid and carefully describes his technic for ligating the internal carotid artery. The cause and prevention of thrombosis and embolism are also considered.

BECK

McQuiston, W. Q.: Anesthesia in Cardiac Surgery: Observations on Three-Hundred and Sixty-Two Cases. Arch. Surg. **61:** 892 (Nov.), 1950.

The author reports some clinical observations relative to anesthesia for 362 patients operated on for congenital heart disease. Relatively large doses of morphine combined with atropine or scopolamine are of value in reducing the nervous irritability of the heart. There was no case of cardiac arrest in this series of 362 cases. Cyclopropane was the anesthetic agent of choice. Reduction of body temperature during operation, especially in the cyanotic group, lessened the number of deaths due to anoxia. There were no deaths among 112 patients undergoing surgical procedures for correction of a patent ductus arteriosus or in 7 patients in whom resection of a coarctation of the aorta was performed. There were nineteen deaths among 83 cyanotic patients below 3 years of age, or a mortality of 22.8 per cent. Only four deaths occurred among 135 similar patients between 3 and 16 years of age, a mortality of 2.9 per cent. The mortality in all patients in whom an anastomosis was done was 10.5 per cent. The over-all mortality was 12.7 per cent. It is obvious, therefore, that if an aortic-pulmonary anastomosis can be done between the ages of 3 and 16 years, the mortality rate can be kept extremely low.

BECK

Moore, H. D.: The Replacement of Blood Vessels by Polythene Tubes. Surg. Gynec. & Obst. **91:** 593 (Nov.), 1950.

A length of thoracic aorta in 20 rabbits was replaced by polythene tubing of 2.5 to 3 mm. internal diameter (except in 2 in which it was 4 mm.). In 13 of the animals, the tubes were patent at the time of death or were patent up to 10½ months after operation. In 8, thrombosis occurred, but in 5 of these the tubes were patent for 1½, 5, 6, 7, and 14 weeks respectively, and in one, thrombosis was caused by errors in technic. Arteriograms on the living animals, and postmortem examinations on those which died showed that the aorta above and below the tube was normal. A fibrous capsule forms rapidly round the tube and a fibrocartilaginous "buttress" forms at the junction of the tube and aorta. Histologic examination in 3 cases showed in the inside of the tube, at the upper end, the beginning of an endothelial lining. The replacement of ten internal jugular veins in 6 rabbits was unsuccessful in all due to thrombosis in the tube. The use of heparin, and of a "silicone" lining and heparin, made no difference to the results.

BECK

Cooley, D. A.: Cardiac Resuscitation during Operations for Pulmonic Stenosis. Ann. Surg. **132:** 930 (Nov.), 1950.

This report deals with attempts at cardiac resuscitation because of imminent or actual cardiac arrest during 48 of 878 operations for pulmonic stenosis. In 33 instances it was possible to restore normal cardiac action, but only 12 of these patients survived to leave the hospital. In 2 of these 12 patients who were otherwise well, there were residual neurologic abnormalities as a result of cerebral ischemia during the cardiac arrest. Cardiac emergencies under anesthesia may be divided into two main types, cardiac arrest and ventricular fibrillation. No instance of ventricular fibrillation was encountered in this series. The management of cardiac emergencies during operation for pulmonic stenosis is discussed and preventive measures outlined.

BECK

Welch, K. J., Johnson, J., and Zinsser, H.: The Significance of Pulmonary Vascular Lesions in the Selection of Patients for Mitral Valve Surgery. Ann. Surg. **132:** 1027 (Dec.), 1950.

Pulmonary vascular lesions may produce secondary obstruction within the pulmonic circuit in patients with long standing mitral stenosis. The significance of these pulmonary vascular lesions in the selection of patients for mitral valve surgery has been given only scant attention in the surgical literature. A patient with mitral stenosis is described in whom pulmonary vascular lesions were present to a marked degree. These seemed to account for failure of the mechanically adequate mitral commissurotomy to relieve the existing circulatory obstruction. Previous observations and a review of the literature suggest that such patients will not derive benefit from surgical measures aimed at the relief of mitral stenosis.

BECK

Brooks, J. W.: Aortic Resection and Anastomosis in Pups Studied After Reaching Adulthood. Ann. Surg. **132:** 1035 (Dec.), 1950.

The studies reported in this paper were undertaken in an attempt to discover if the site of anastomosis in the immature aorta failed to increase in diameter. Should this be so, the eventual outcome would be a stricture, relatively and actually, of serious degree.

The aortas of 28 pups were resected and immediately anastomosed; using a continuous, everting mattress suture of 5-0 silk, which penetrated all layers of wall. Subsequent studies, during life and after sacrifice, indicate that the point of anastomosis will increase in size as the puppy grows, but not as much as normal portions of the aorta. The degree of constriction was 17 to 20 per cent at the site of anastomosis. The degree of constriction was not sufficient to stimulate increased development of collateral channels or to cause cardiac enlargement. Healing at the point of anastomosis was excellent and adequate to withstand normal aortic pressures. Six of the dogs are being kept for study over a longer period in an attempt to determine the final result of this surgical procedure.

BECK

Gagnon, E. D.: Commissurotomy in Mitral Stenosis. Canad. M. A. J. **63:** 537 (Dec.), 1950.

Commissurotomy, as described by Baley, Glover, and O'Neill, was performed in 3 patients with severe mitral stenosis. The longest follow-up in this report is 10 months. The first 2 patients were young men who were totally incapacitated, one of whom showed calcification of the mitral valve. These 2 improved to the point where their exercise tolerance was at least double their preoperative capacity. One of them has resumed normal activity and work.

The third patient died 48 hours postoperatively. Autopsy revealed that the incision had been placed slightly anterior to the commissure, and had incised the aortic cusp. This patient was a poor operative risk because of a right hemiplegia of three years duration and auricular fibrillation.

WAIFE

DeBakey, M. E., Creech, O., and Woodhall, J. P.: Evaluation of Sympathectomy in Arteriosclerotic Peripheral Vascular Disease. J. A. M. A. **144:** 1227 (Dec.), 1950.

The authors report 146 consecutive cases of arteriosclerotic peripheral vascular disease of the lower extremities treated by lumbar sympathectomy. The procedure was bilateral in 55 cases, so that altogether 201 sympathectomies were done. Each sympathectomy involved the removal of all the lumbar sympathetic ganglions and chain overlying the second to the fourth lumbar vertebrae. All patients were followed at least six months, 75 per cent for more than one year, and 38 per cent were followed more than two years. Eighty-five per cent of cases with no gangrene responded well and 75 per cent of cases with impending gangrene were likewise improved. Definite improvement was noted in 35 per cent of cases with frank gangrene. Comparison of diabetic and nondiabetic groups reveal no difference except where a higher incidence of extremity improvement was observed among the diabetic patients with frank gangrene. There were no operative deaths in the entire series and age was not a contraindication. The authors feel that sympathectomy is the method of choice in the treatment of arteriosclerotic peripheral vascular disease unless severe cardiac, renal, cerebral or pulmonary disease is present.

KITCHELL

THROMBOEMBOLIC PHENOMENA

Askey, J. M., and Cherry, C. B.: Thromboembolism Associated with Auricular Fibrillation. J. A. M. A. **144:** 97 (Sept.), 1950.

The authors point out that 45 per cent of cases with rheumatic heart disease and auricular fibrillation have mural cardiac thrombi as compared to 15 per cent of individuals who have normal rhythm. They point out that there are certain hazards and difficulties in the use of continuous anticoagulant therapy. The authors have treated 20 patients with heart disease and auricular fibrillation. Ten of these were rheumatic and 10 were nonrheumatic. The period of follow-up has been from two months to over two years in the 20 patients. In 13 of the 20 patients embolism had occurred prior to the institution of dicumarol, and in 7 of these cases embolism had been repeatedly noted. In the remaining 7 cases no previous emboli had appeared and dicumarol was administered to prevent intracardiac clot formation. During treatment 4 of the patients had repeated emboli. The authors fell that these episodes are explained by the fact that certain clots

were present before dicumarol therapy was started, by the fact that the prothrombin level might not have been maintained at an effective level, and third because intracardiac clots may have formed despite a desirable prothrombin level of the blood. The authors conclude that the incidence of thromboembolism in the patients presented appears to have been decreased from that anticipated on a statistical basis.

KITCHELL

Laufman, H., Gobrewski, R., Treger, N. V., Method, H., and Tanturi, C. A.: The Significance of the Blood "Sludge" Phenomenon. Quart. Bull. Northwestern Univ. M. School **24:** 257, 1950.

This article is a critical review of the phenomenon of intravascular erythrocyte clumping, termed "sludging," and an attempt to separate the wheat of proved fact from the chaff of untested hypothesis and unjustified conclusions.

Sludging, observable by direct microscopy of the small vessels of the bulbar conjunctiva, occurs in a wide variety of pathologic states (infections, shock, hypertension, burns, anoxia, etc.), but is found also in many apparently normal individuals. The degree of sludging may vary considerably in a given individual from day to day, and, in disease states, bears no relation to the severity of the disorder. Well-developed sludging, hyperglobulinemia, and rapid erythrocyte sedimentation are frequently associated. Heparin and dicumarol in the experimental animal may prevent the thrombosis occurring with sludging, but have no effect on the sludging itself.

At present, the basic mechanisms resulting in sludging remain unidentified, and the possible importance of the phenomenon in the pathogenesis of disease is unknown.

HANNO

VASCULAR DISEASE

Addis, H. St. C. C., Jepson, R. P., and Kellgren, J. H.: On the Effect of Arterial Occlusion and Venous Congestion upon Limb Pain. Clin. Sc. **9:** 271 (Aug.), 1950.

Ten minute periods of arterial and venous occlusion were applied separately to extremities in which a painful state had resulted from a variety of pathologic lesions. In patients with deep closed suppurations there was a considerable, and usually dramatic, increase of pain during arterial occlusion. Venous occlusion only rarely produced an increase in pain. In a wide variety of other painful states neither arterial nor venous occlusion caused any increase in pain.

In 7 patients with infection of the finger tip it was observed that, during arterial occlusion, pain appeared earlier and increased more rapidly at higher than at lower temperatures.

WESSLER

Winsor, T.: Influence of Arterial Disease on the Systolic Blood Pressure Gradients of the Extremity. Am. J. M. Sc. **220:** 117 (Aug.), 1950.

The pneumoplethysmograph was utilized to study blood pressure at various sites on an extremity in a series of patients with peripheral vascular disorders and in a control group. In normal subjects, the blood pressures were found to be higher on all points of the lower extremity than on comparable points of the upper, with a thigh-to-toe pressure drop of 40 mm. Hg, and calf-to-ankle drop of 12.5 mm. Hg. In those patients with aortic obstruction, the reverse was found to be true. Similarly, obstruction of one iliac artery showed pressures which were lower at all points on the involved, as compared with the uninvolved, side. In the cases with arterial vascular disease, the position of the marked pressure drop on the curve indicated the approximate site of the obstructing lesion. The drop in pressure distal to the obstruction amounted to as much as 50 to 60 mm. Hg.

ABRAMSON

Angelman, H., Hall, E. G., and Spencer, R.: The Syndrome of Obstruction of Inferior Vena Cava in Childhood. Brit. M. J. **2:** 752 (Sept.), 1950.

The authors review developmental obstruction of the vena cava in 2 infants and thrombosis in one. In one the deep venous collaterals as well as the vena cava were obstructed as indicated by the presence of enlarged superficial veins in the abdominal wall. Edema of the limbs on effort and the presence of a dilated internal saphenous vein suggested involvement of the iliacs. No kidney involvement was demonstrated. The thrombotic obstruction case presented partial obstruction of the left common femoral and iliac veins and this was demonstrated by a venogram and terminated fatally.

The authors give a good and hopeful prognosis in those with uncomplicated developmental vena caval obstruction without restricting the children's activities. They feel that in later years varicose ulcers may develop and that, should pregnancy occur, it may aggravate the underlying pathology. Both living patients are symptom free.

TANDOWSKY

McKelvey, J. L.: Arteriosclerotic Pregnancy Toxemia. Am. J. Obst. and Gynec. **60:** 510 (Sept.), 1950.

The author discusses the subject of permanent hypertension which arises during pregnancy and is associated with toxemia. In some patients the disease is relatively benign, while in others the progress of the condition may be rapid, particularly when repeated pregnancies occur. In the latter group, uremia may develop and the patient may die of cardiac and kidney failure. According to the author, an appropriate name for this condition is arteriosclerotic pregnancy toxemia. At autopsy, vascular

lesions are generally found in the arterioles of the kidney, central nervous system, adrenal gland and pancreas. When uremia occurs terminally, signs of malignant nephrosclerosis are also noted. One is unable to distinguish between the vascular lesions of arteriosclerotic pregnancy toxemia and those present in essential hypertension. Pathologic changes are widely spread throughout the body.

Hypertensive toxemias are observed in approximately 5 per cent of pregnancies and of this number, about 40 per cent are arteriosclerotic in type. It is the opinion of the author that, as prophylaxis, prolonging the hypertension of pre-eclampsia must be avoided, particularly when this is of a severe degree. It has been shown that the duration of this type of hypertension is directly related to the frequency of arteriosclerotic pregnancy toxemia. Furthermore, it is wiser not to permit women with a diastolic blood pressure of 100 or over to undertake a subsequent pregnancy. If this has already occurred, therapeutic abortion should be considered.

ABRAMSON

Lindskog, G. E., Liebow, A., Kausel, H., and Janzen, A.: Pulmonary Arteriovenous Aneurysm. Ann. Surg. **132:** 591 (Oct.), 1950.

The authors present 4 cases of pulmonary arteriovenous aneurysm. Three were treated by lobectomy and the pathologic anatomy of the lesions was studied by means of the vinylite-plastic injection technic. The clinical and pathologic features of the syndrome are reviewed.

WESSLER

Glass, W. H.: Rutin Therapy in Diffuse Capillary Bleeding: Ineffectiveness When Fragility Tests Are Normal. Am. J. M. Sc. **220:** 409 (Oct.), 1950.

The author reports that the use of rutin in 5 cases of hereditary hemorrhagic telangiectasia with normal capillary fragility tests, in adequate doses for two to three years, has not yielded any objective therapeutic result. By contrast, one instance is presented with diffuse capillary permeability of undetermined etiology, in which a markedly increased Rumpel-Leede and Gothlin index were observed. The patient responded to rutin with a definite decrease in her "capillary fragility" indexes.

DURANT

Nelson, L. E., and Kremen, A. J.: Experimental Occlusion of the Superior Mesenteric Vessels with Special Reference to the Role of Intravascular Thrombosis and Its Prevention by Heparin. Surgery **28:** 819 (Nov.), 1950.

The authors discuss briefly the literature on experimental mesenteric vascular occlusion. Under phenobarbital anesthesia, normal dogs were subjected to laparotomy. The superior mesenteric artery alone was occluded in one group, the vein occluded in another group, and both artery and vein occluded in a third group. The effects of occlusion of the superior mesenteric artery and vein are discussed. The cause of death from arterial occusion is peritonitis and occurs from 12 to 20 hours after the vessel is clamped. When the superior mesenteric vein is occluded, death occurs within four hours from shock. The superior mesenteric artery or vein can be safely occluded for two hours. Continued interruption is dangerous. The use of sulfasuxidine or streptomycin to reduce the intestinal bacterial flora before surgery extends somewhat the time of safe occlusion. Heparin administered preoperatively to prevent intravascular clotting produced extension of the time of safe occlusion and was particularly effective in the case of venous occlusion. The superior mesenteric vein was ligated in 8 heparinized dogs and 6 animals survived.

BECK

Luke, J. C.: Evaluation of the Deep Veins following Previous Thrombophlebitis. Arch. Surg. **61:** 787 (Nov.), 1950.

Retrograde venography of the deep veins of 18 patients with a history of previous deep thrombophlebitis and evidence of one of the complications of the postphlebitic leg showed deviations from the normal in all. In 12 cases there was loss of function or actual disappearance of the valves of the deep veins; in the remaining 6 cases recanalization of a thrombus in the main vein was noted. In practically every venogram there was evidence of dilatation and tortuosity of the collateral venous channels. In 4 patients in whom venography could not be carried out, exploration showed that the lumen of the common femoral vein had been obliterated. The author emphasizes the fact that since there was no correlation between the severity of the venous damage and the occurrence, degree, or extent of the postphlebitic complications, ligation of the deep veins would have been unsound.

Although under certain conditions surgical approach to varicose veins, lumbar sympathectomy for sympathetic overactivity, and excision and skin grafting of ulcers are of benefit to these patients, the author believes that the basic therapy is one of medical management, consisting of the proper use of elastic stockings, elevation of the leg, and an understanding by the patient of the limits placed on his activities by his disease. The specific instructions given to patients are listed.

WESSLER

Ortner, A. B., and Griswold, R. A.: Chronic Occlusion of the Bifurcation of the Aorta. Arch. Surg. **61:** 793 (Nov.), 1950.

The authors discuss the pathology, clinical picture, prognosis, and treatment of chronic occlusion of bifurcation of the aorta. They present 3 cases. In the first case symptoms were relieved following unilateral lumbar sympathectomy. In the second pa-

tient clinical improvement followed two operations in which bilateral lumbar sympathectomy, and resection of the terminal aorta and iliac vessels were carried out. In the third patient, in whom only the left iliac system was completely occluded, symptomatic improvement followed left sympathetic ganglionectomy and resection of the left common iliac and proximal portions of the left internal and external iliac arteries.

WESSLER

Julian, O. C., and Shabart, E. J.: Lumbar Sympathectomy in Peripheral Vascular Disease. Arch. Surg. **61**: 804 (Nov.), 1950.

Among 52 patients with intermittent claudication secondary to arteriosclerosis, 25 noted some improvement in claudication persisting six months to three years after sympathectomy. Similarly 12 of 20 patients with thromboangiitis obliterans showed some improvement in claudication.

Sympathectomy provided some relief from rest pain in 37 of 52 patients with arteriosclerotic disease and in 12 of 15 patients with thromboangiitis obliterans. In no instance did sympathectomy relieve neuritic pain.

Healing of ulcerations on the skin of the feet occurred in 3 of 5 patients following sympathectomy.

WESSLER

Tobin, C. E., and Zariquiey, M. O.: Arteriovenous Shunts in the Human Lung. Proc. Soc. Exper. Biol. & Med. **75**: 827 (Dec.), 1950.

The authors performed this experiment utilizing the glass sphere technic followed by injection media, to ascertain the presence and anatomic location of arteriovenous shunts in the human lung. Arteriovenous shunts, many times the accepted diameter of capillaries, were demonstrated in isolated human lungs with little or no pulmonary pathology, by the passage of glass spheres from the pulmonary artery to or through the pulmonary veins. The injection of these vessels with liquid latex or vinyl acetate indicated that the shunts were located at the apex of and within the lobular divisions of the lungs. Smaller shunts were located at the level of the smaller bronchi and respiratory bronchioles and near the alveolar sacs and alveoli and also in the pleura. No shunts were found in the hilar regions nor along the course of the larger branches of the pulmonary artery and vein.

MINTZ

OTHER SUBJECTS

Kuechmeister, H., and Schaerfe, W.: The Capillary Resistometer, a Device for the Measurement of Capillary Resistance, and Its Clinical Application. Deutsche med. Wchnschr. **75**: 316 (March), 1950.

The authors describe an apparatus for the measurement of cutaneous capillary resistance by graduated suction on a circumscribed area of the skin. When a negative pressure of 300 mm. Hg is applied to an area 2 cm. in diameter, petechiae appear in the normal subject following suction of 11 to 15 seconds duration. In patients with essential hypertension, this critical time was between 6 and 11 seconds. The time could be changed to normal values by daily use of rutin (120 to 300 mg.), but returned to the previous values following cessation of medication.

PICK

Burchell, H. B.: An Introduction to the Clinical Applications of Oximetry. Proc. Staff Meet. Mayo Clin. **25**: 377 (July), 1950.

Photoelectric determinations of the oxygen saturation of the arterial blood by the application of an ear oximeter have been used in many different ways. There have been two main developments in oximetric technic; one pertains to measurement of the arterial oxygen saturation in the intact ear, the other to the oxygen saturation of a sample of blood obtained by a whole blood cuvette. The incorporation of an oximeter with a miniature light source and photoelectric cell into the distal end of a cardiac catheter or "sound" has been developed and has promise. It should reflect the oxygen saturation of the blood whenever the tip of the sound is placed within the vascular system.

In one case studied the diagnosis was patent ductus arteriosus and an associated intracardiac defect. The arterial oxygen saturation remained normal after the thorax was opened and the lung collapsed. When the ductus arteriosus was closed, there was no unexpected drop in arterial oxygen saturation. During surgery it was necessary to aspirate the tracheobronchial tree frequently, and there was a marked arterial desaturation. In the last instance, the arterial oxygen saturation dropped to about 20 per cent. This suggests that the blood passing through the lungs was losing oxygen to the air being aspirated.

Induced hypoxemia by low oxygen mixtures is, on occasion, a useful test in the diagnosis of coronary insufficiency. By the use of the oximeter, a considerable difference has been demonstrated in the arterial oxygen saturation of patients breathing the same oxygen-nitrogen mixture, which in this study was 10 per cent oxygen. The degree of hypoxemia, however, was shown by the oximeter not to be the only factor determining the presence or absence of a positive result in patients with coronary disease.

The oximetric cuvette has been of great value in cardiac catheterization, allowing more frequent sampling through the catheter and a more confident attitude toward differences in the values between samples, differences which by the gasometric type of determination might not be significant.

SIMON

BOOK REVIEWS

Les Maladies des Coronaries. L'infarctus du myocarde. L'insuffisance coronarienne, ed. 2. *Ch. Laubry and P. Soulie.* Paris, Masson et C^ie^, 1950. 618 pages, 299 figures.

The authors have rewritten their original treatise, first published in 1943 during the occupation, in an effort to bring it up to date. Probably the most useful portion of this edition is a very comprehensive review of electrocardiography, which is almost entirely inspired by the writings of Wilson and his school. The presentation of this material, however, is occasionally too complex and there is a tendency to overemphasize the value of vectorcardiography at the expense of some of the more practical clinical points.

In the preliminary discussion of the coronary circulation the authors are at variance with the usual concepts of the mechanical as well as other factors regulating coronary blood flow, constantly re-emphasizing the dominant role of the vegetative nervous system in regulating all aspects of the coronary circulation, and apparently are not aware of the more recent publications on this subject. Indeed the bibliography of the entire volume is somewhat dated.

The largest portion of the book is given over to a clinical presentation of the various aspects of coronary disease. The syndromes are often brilliantly and vividly described, but unfortunately there is much that is repetitious and even arbitrary. Criticisms directed at newer interpretations are unsupported by factual data and one can almost at times detect a faint mistrust of the theory in vogue and a tendency to cling to the older local traditional concept. The chapter on differential diagnosis is too brief to be of help to the student or practitioner and contains a minimum of clinical discussion. For example, nowhere in the book is there any indication of the frequency with which certain findings, such as fever or a lowered blood pressure, appear in patients with myocardial infarcts. Statistics are everywhere avoided. Indeed, the reader is cautioned against their persuasive influence in any conclusions which might be drawn.

The organization of the subject as a whole is not consecutive; the first two chapters contain excellent material on the normal anatomy of coronary circulation while the pathologic anatomy is not presented until after the clinical discussion. The microscopic sections are well defined but the gross pathology is almost impossible to detect due to the poor quality of paper upon which the illustrations appear.

The chapter on therapy is somewhat limited, and its recommendations quite different from those which would be found in this country. Injections of camphor and the use of ice on the precordium are highly recommended. Little critique of newer forms of therapy is given. Nonetheless these are, for the most part, regarded with skepticism, and dicumarol and Demerol are warned against as dangerous, although no detailed reasons are given for reaching this conclusion.

One has the feeling in reading this monograph that it represents a transitional stage in which the authors, loathe to part with the traditional, are nonetheless attracted by the newer literature. The volume is much too long and one would hope that in the next edition the material could be condensed and the more recent ideas, in particular physiologic concepts in which the book is very deficient, could be given more adequate presentation. The present volume represents a tremendous effort to rouse the French reader from the literary isolation of the war period and although acceptance of the newer concepts in diagnosis and therapy is slow and reluctant, their presentation to the reader is attempted.

ANDRÉ COURNAND AND M. IRENÉ FERRER

Praktische Elektrokardiographie ed. 3. *Franz Kienle.* Stuttgart, Georg Thieme Verlag, 1950. 448 pages, 426 illustrations, 38 DM.

This large volume on clinical electrocardiography is written entirely on the basis of the author's personal viewpoints, which stem from extensive clinical experience. Scant references are made to a few theoretic considerations advanced years ago by Weber, Schellong and Schütz. The text is easily written, studded with interesting case material and is profusely and well illustrated. Type setting and reproductions are excellent.

The volume will be welcome to those who enjoy authoritative rules and empirical dogmatism. Those who believe that the subject matter should be taught from the vantage point of basic information on electrical events in cardiac tissue will be disappointed. A thorough understanding of the physiologic basis of the electrocardiogram, as developed in the texts of Burch and Winsor, and of Wolff, although at first more difficult to digest, should ultimately lead to a more rational clinical interpretation of records by the reader. There is no doubt, however, that the crowd will follow the easier paths.

For the American reader, the absence of sections on vectorcardiography and gradient analysis, and the extremely sketchy presentation of precordial electrocardiography in an appendix are true

anachronism and are singled out over a host of minor inaccuracies mostly stemming from the approach chosen by the author. The only references cited by the author are his own; the compilation of a more complete bibliography should enhance the value of the book as a reference text.

HANS H. HECHT

The Physiological Basis for Oxygen Therapy. *Julius H. Comroe, Jr., and Robert D. Dripps.* Springfield, Charles C Thomas, 1950. 85 pages, 1 figure, 1 table. Price, $2.00.

This monograph, one of a series, is divided into four parts dealing with (1) the effects of oxygen inhalation in normal man; (2) anoxia, its etiology, diagnosis, and treatment; (3) oxygen inhalation in conditions without anoxia; and (4) the possibilities of harm from the inhalation of oxygen.

Although not a "technic" book, this short and well-written monograph by two well known investigators furnishes a fine background for the rational use of oxygen. It is recommended highly to both students and physicians.

MORRIS W. STROUD, III

Clinical Electrocardiography. *Francis F. Rosenbaum.* Oxford University Press, New York, 1950. 205 pages, 82 figures. $4.50.

This book is reprinted from Oxford Loose-Leaf Medicine. "An attempt has been made in the material presented here to give the reader some understanding of the principles upon which electrocardiography is based and to indicate the place of this method of study in the clinical practice of cardiology."

The large numbers of works on electrocardiography may be graded as to clarity and completeness of presentation. The present book is among the best. The modern conception of the genesis of the electrocardiogram is well presented and the physician now is able to interpret his records by reason rather than by rote. While this volume is not a large one, the discussion and the coverage of the subject are broad. The bibliography enables the reader to refer to much of the important source material. The format and the illustrations are excellent. The reviewer warmly recommends this new presentation, both to students and to physicians.

HAROLD FEIL

Heparin and Heparinoids; Dicumarol. *T. Halse.* Zurich, S. Hirzel Verlag, 1950. 225 pages, 38 figures, 22 tables. 13.50 francs.

This monograph represents the first comprehensive review on anticoagulants in the German language. The author describes the history of the discovery of heparin and dicumarol, the physiologic actions of these substances, the tests used for controlling these actions, the indications and contraindications for their clinical use. His own experience is based on the use of these substances in surgical patients and agrees with that of the majority of other investigators.

The book is of interest particularly because of two sections. In one of these the author describes experiments in vitro and in vivo which, in his opinion, demonstrate clearly a fibrinolytic action of heparin. Different heparins show this action in a different degree. The importance of such an effect—if confirmed—is obvious. In another section the action of a synthetic heparinoid (polysaccharides esterified with sulfuric acid) is discussed. This substance, called Thrombocid, is a cheap and efficient synthetic substitute for heparin. There is no doubt that with two daily intramuscular injections of Thrombocid, one can easily double the coagulation time. The author seems to minimize, however, the marked alopecia which occurs six to eight weeks after cessation of treatment. This is an unexplained side effect which should caution against the widespread use of Thrombocid in spite of the experience that the hair grows again after variable periods. Thrombocid was also found to be fibrinolytic. It depresses the phosphatides in the blood.

The author does not see advantages in the use of Tromexan in place of dicumarol. He discusses the influence of the autonomic nervous system on the prothrombin level, the postoperative changes of this level as well as the changes found at the time of a thrombosis.

The action of dicumarol on capillary permeability, the use of heparin in anaphylactic shock and as a stabilizing agent in blood transfusions is discussed.

SCHERF

The Cerebral Circulation in Health and Disease. *Carl F. Schmidt.* Springfield, Charles C Thomas, 1950. 78 pages, 12 figures, 2 tables. $2.00.

The anatomic arrangement of the blood vessels of the brain is in many respects unique and there have been many misunderstandings as to how these vessels function. Up to 1928 it was generally believed that the brain, the most delicate of all organs, was totally at the mercy of the systemic circulation as far as its blood supply was concerned. Since then it has been shown that the cerebral vessels are subject to all the influences which affect blood vessels elsewhere in the body: innervation, hormones and other chemical products, especially oxygen and carbon dioxide. In short, the intrinsic control of the cerebral circulation is an extraordinarily sensitive mechanism. But the brains of laboratory animals are not like the brain of man, and satisfactory quantitative methods were not developed for studying the problem in man until the work of Gibbs in 1947 and of Kety in 1948. Gibbs' method is based on an adaptation of the Stewart dye-dilution principle. It has the advantage that it can be done quickly, without the 10 minute period of steady inhalation required by Kety's procedure. But injections into one carotid send more

dye to the ipsilateral hemisphere than to the contralateral, so the outflow from both jugular veins should be collected and the readings averaged to get cerebral blood flow.

Kety, working in Schmid's laboratory, developed a method which made possible the quantitative measurement of cerebral blood flow and cerebral metabolism in intact man. Nitrous oxide was used and its uptake by the brain was measured on the Fick principle. The method has proved to be theoretically sound and clinically practical. The average normal blood flow in the brain is found to be 54 cc. per 100 Gm. of brain per minute. Determinations made on normal subjects under varied conditions and on patients with different diseases show the ability of normal human cerebral vessels to adjust their tonus to the metabolic requirements of the brain, in relation to either the pressure or the chemical composition of the blood coming to them. Hyperventilation with alkalosis caused a marked decrease in blood flow. Increased carbon dioxide caused the most marked increase observed, except in cases of hemangioma with arteriovenous communication. Abnormally high tensions of oxygen cause a diminution in blood flow by vasoconstriction. Low oxygen acts like carbon dioxide, but to a lesser extent. In schizophrenic patients blood flow, oxygen consumption, arteriovenous difference and vascular resistance all fall within normal limits. In hypertensive patients a practically perfect cerebral homeostasis is also maintained, while senile and arteriosclerotic dementia show decreased flow and decreased oxygen consumption.

This is an excellent little book, carefully prepared, well written, with a good bibliography.

STANLEY COBB

Introduction to the Regulation of Blood Pressure and Heart Rate. *Corneille Heymans.* Springfield, Charles C Thomas, 1950. 60 pages, 25 figures, $2.00.

The author, in a short monograph, clearly presents the various nervous reflexes concerned with the regulation of heart rate and blood pressure. He dwells especially on the pressoreceptors in the cardio-aortic area and in the carotid sinus which are sensitive to the slightest change in blood pressure. From the pressoreceptors in these areas afferent impulses are transmitted to the vasomotor center in the medulla over the glossopharyngeal and vagus nerves. If the blood pressure rises the heart is reflexly slowed, the cardiac output is reduced and peripheral vasodilatation occurs. If the blood pressure falls the corollary occurs. Other reflexes are discussed. The physiology for the maintenance of the circulation is well illustrated by numerous diagrams. There is the suggestion that we will find the answer to clinical hypertension by further understanding the pressoreceptors and the reflex changes which they initiate.

The clinician will find this monograph an interesting review and the student will enjoy the clear presentation of the nervous reflex arcs surrounding the heart and great vessels.

JOSEPH A. WAGNER

Selected Studies on Arteriosclerosis. *Rudolf Altschul,* Springfield, Charles C Thomas, 1950 163 pages. $5.50.

"This title of the present book was chosen intentionally to indicate that this is a collection of various studies on arteriosclerosis. . . . It deals both with human and with experimental arteriosclerosis. . . . The book makes no pretense of being either a review or a final and complete report on arteriosclerosis." Despite these introductory remarks by the author there is much excellent material in the book of a histopathologic nature that should be of value to students of arteriosclerosis and especially to research workers in that field. The author gives the results of his own researches and compares them with the work of others. The book is beautifully written, and the photomicrographs are superb. In the short "Summary and Comment" the aims of the various chapters are given as follows: "(a) to bring out more distinctly some unsolved morphological problems in human and experimental arteriosclerosis; (b) to attempt an accurate analysis of cellular pathology in various angiopathies and to correlate them; (c) to report on findings in human and in experimental arteriosclerosis which had hitherto been overlooked; and also to describe results in experimental cholesterol arteriosclerosis which had not previously been obtained; and (d) to modify the technique of experimental arteriosclerosis with the idea of obtaining new results."

In Chapter VII the author states: "The extensive work done on experimental arteriosclerosis has so far thrown little if any light on the problem of human arteriosclerosis." To one like the reviewer, a clinician who has dabbled in the field of cardiovascular pathology, the book certainly brings out the complexities and vastness of the problem of the etiology and pathogenesis of human arteriosclerosis. To a pathologist working on this problem the book should be helpful.

WALLACE M. YATER

Thromboembolic Conditions and Their Treatment with Anticoagulants. *Charles D. Marple and Irving S. Wright.* Springfield, Charles C Thomas, 1950. 418 pages.

This volume is an attempt on the part of the authors "to provide a convenient summary of some of the pertinent information collected during the past decades regarding thromboembolic phenomena and the use of anticoagulants in the treatment of them. . . ." The authors are well qualified for the task which they have undertaken. The scope of this volume is indicated by the titles of the various sections which follow: "Thromboembolic Phenomena in

Clinical Medicine," "The Mechanism of Intravascular Clotting," "Rationale for the Use of Anticoagulants," "The Use of Anticoagulants Clinically," "Technics for the Administration of Anticoagulants," "Hemorrhage Due to the Use of Anticoagulants and Its Management," "Failures and Abuses of Anticoagulant Therapy," "Physiologic and Pharmacologic Influences," "Miscellaneous Observations," and "Recent Developments." There are appendixes on methods for determining coagulation time, prothrombin time and prothrombin clotting time, and on protamine titration. There are also 684 references and an excellent cross index.

The authors have indicated the difficulty in writing a book which is completely up-to-date on a subject which is so dynamic, and they have added to the original manuscript a section of 107 pages entitled "Recent Developments." The volume would be somewhat better if this portion had been integrated into the original manuscript, but the difficulties of such a procedure are great. The delay between the writing of the manuscript and its publication has necessitated omission of consideration of 4-hydroxycoumarin anticoagulant No. 63, but, otherwise, the volume seems almost as timely as a daily newspaper.

It is the reviewer's pleasure to recommend this monograph without reservation. It is an excellent reference source and is characterized by meticulous and careful preparation. Evaluation of data is conservative and stamps the authors as both critics and students.

It is improbable that many physicians with no prior experience with anticoagulants could use them judiciously and expertly as a result of reading this book, but this is no fault of this volume. It is certainly true that every physician, except an expert in this field, who contemplates using anticoagulants or has used them would benefit enormously from reading this volume. Even the expert will be pleased by the extensive references and the thorough preparation.

EDGAR V. ALLEN

Tomografia Clinica Cardio-Vascular. *Juan Govea and Fidel Aguirre.* Vol. 29, Biblioteca del Medico Practico. Havana, Cuba, Cultural S.A., 1949. 485 pages, 308 figures, $8.00.

This rather extensive monograph (written in Spanish) represents the largest and the most complete compilation on the application of tomography (planigraphy) to cardiovascular disease. The brief chapter on technic indicates that sections used in their studies were about 1 cm. apart. The chapters on normal anatomy and positions (posteroanterior, right and left anterior obliques, and left lateral) are treated in the conventional manner, introducing concepts of depth as well as height and width. The anterior position of the right ventricle in contrast to the posterior position of the bulk of the left ventricle is strikingly demonstrated. Structures such as the left and right atria, the pulmonary veins, the bronchi and the aorta also can be demonstrated, though some of the illustrated examples require imaginative interpretation, probably due to the loss of contrast in the process of their reproduction.

Differentiation of right and left ventricular enlargement is stressed throughout. This is particularly important in congenital heart disease with rounding of the lower left cardiac contour when right ventricular enlargement is suspected. Two instances of the apparent demonstration of a patent ductus arteriosus, one of which also had an aortic funnel-like bulge, similar to that demonstrable by angiocardiography, deserve special mention. In a case of coarctation of the aorta the site of narrowing is well demonstrated. Other uses of tomography were in demonstrating calcifications of the aorta, aneurysms, dilatation of the pulmonary artery, extracardiac masses, and mediastinal tumors.

On the whole the book stands up rather well, and should stimulate further use of the method. As indicated above, the illustrations are not always clear, but in a number of instances they are supplemented by accompanying diagrams. The bibliography is sketchy, and not too accurate; the legends do not indicate precise depths and at times do not conform to the theme of the accompanying chapter. However, these criticisms are minor in character and should not substantially detract from the value of this book.

JOHN B. SCHWEDEL

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A. H. A. FELLOWSHIPS

Applications for Established Investigators and for Research Fellows must be received by September 15, 1951. Information and forms may be obtained from the Medical Director.

CAREER INVESTIGATOR NAMED

Dr. Victor Lorber, Associate Professor of Biochemistry, Western Reserve University Medical School, Cleveland, has been appointed as the Association's first Career Investigator. Dr Lorber was unanimously selected by a subcommittee of the Executive Committee of the Scientific Council. He will receive a starting annual stipend of $12,000 and will be free to engage in research of his own choosing in the cardiovascular field.

Dr. Lorber may work in any institution in the United States that offers adequate facilities. In addition to his annual stipend, a maximum of $7,500 per year will be made available for technical assistance and supplies. The institution at which he chooses to work will receive $1,000 annually for overhead.

In announcing Dr. Lorber's appointment, Dr. Louis N. Katz, President, pointed out that this is the first of a series of Career Investigatorships which the Association plans to establish, depending on increasing financial support from the public. This new type of research support, Dr. Katz said, has long been advocated by leading scientists, making it possible for investigators to devote life-long careers to medical research.

Dr. Lorber was born in Cleveland in 1912, was graduated from the University of Chicago in 1933, and interned at the Michael Reese Hospital in Chicago from 1937 to 1938. He served as Assistant Professor, Department of Physiology, University of Minnesota from 1944 to 1946, when he joined Western Reserve. Dr. Lorber has been working on a study of the metabolism of the heart muscle utilizing isotope technics, and recently received a grant-in-aid from the Association in support of this project.

AFFILIATE RESEARCH SUPPORT

Additional affiliate support for the national research program has been received from the Cleveland Area Heart Society which has agreed to finance the grant-in-aid awarded to Western Reserve University (Arnold Lazarow) for the period July 1, 1951 to June 30, 1952, in the amount of $4,200. This grant will continue a study of the interrelationship between vascular disease and diabetes.

"EXAMINATION OF THE HEART"

A revision of the booklet, "Examination of the Heart," first published by the Association in 1940, is now available to interested physicians. The revision was completed by a committee under the Chairmanship of Dr. Harry E. Ungerleider, New York. The Recording and Statistical Corporation of Boston has printed 25,000 copies of the revised manual at no cost to the Association and this initial quantity will be distributed free.

EXECUTIVE COMMITTEE

The following members of the Board of Directors have been named to the Executive Committee: Edgar V. Allen, M.D., Rochester, Minn.; E. Cowles Andrus, M.D., Baltimore; Mrs. Alben W. Barkley, Washington; Bruce Barton, New York; Alva Bradley, Cleveland; William H. Bunn, M.D., Youngstown; S. DeWitt Clough, North Chicago; George K. Fenn, M.D., Chicago; Frank N. Isbey, Detroit; T. Duckett Jones, M.D., New York; Louis N. Katz, Chicago; Grant Keehn, New York; Robert L. King, M.D., Seattle; R. Bruce Logue, M.D., Emory University, Ga.; H. M. Marvin, M.D., New Haven; Robert L. Mehorney, Sr., Kansas City; A. W. Robertson, Pittsburgh; John J. Sampson, M.D., San Francisco; Harry A. Schroeder, M.D., St. Louis; Howard B. Sprague, M.D., Brookline, Mass.; Frederick K. Trask, Jr., New York; Robert W. Wilkins, M.D., Boston; Irving S. Wright, M.D., New York.

SCIENTIFIC COUNCIL MEMBERSHIP

To broaden the membership of the Association's Scientific Council, the following resolution has been approved by the Board of Directors:

"That all present members of the Scientific Council shall continue their membership in the Council; all medical members of the American Heart Association and its affiliates may become members of the Scientific Council; and other professional persons shall be eligible for election in accordance with Article III of the Rules and Regulations of the Scientific Council."

COMMITTEE ON CARDIOVASCULAR CLINICS

Dr. Herbert Chasis, Associate Professor of Medicine, New York University College of Medicine, has been elected Chairman of the Association's Committee on Cardiovascular Clinics, and Dr. Edward F. Bland, Massachusetts General Hospital, Boston, has been named Vice-Chairman.

A meeting of representatives of local Committees with the National Committee is planned for next January.

COUNCIL ON HIGH BLOOD PRESSURE RESEARCH

The Council on High Blood Pressure Research of the Association has re-elected all of its officers. They include Alva Bradley, President; W. H. Gerhauser, Vice-President; Adrian D. Joyce, Vice-President; George E. Merrifield, Secretary; I. F. Freiberger, Treasurer. All are from Cleveland. Robert W. Wilkins, M.D., Boston, has been re-elected Chairman of the Council's Medical Advisory Board, and E. V. Allen, M.D., Rochester, Minn., has been renamed Vice-Chairman.

COUNCIL ON RHEUMATIC FEVER AND CONGENITAL HEART DISEASE

The American Council on Rheumatic Fever has approved change of its name to the Council on Rheumatic Fever and Congenital Heart Disease.

Dr. Arthur C. De Graff, Professor of Therapeutics, New York University College of Medicine, has been elected Chairman of the Council. Dr. John P. Hubbard, Assistant Professor of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, has been named Vice-Chairman. T. Duckett Jones, M.D., New York, retiring Chairman of the Council; Edwin L. Harmon, M.D., Valhalla, N. Y.; and H. M. Marvin, M.D., New Haven, have been elected to the Executive Committee.

NEW AFFILIATES

Direct affiliation has been approved by the Board of Directors for the New Hampshire and South Dakota Heart Associations. Direct affiliates now total 55, with more than 250 chapters.